Exhibit C

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MDL No. 2789
Honorable Claire C. Cecchi

IN RE: PROTON-PUMP INHIBITOR PRODUCTS LIABILITY LITIGATION (NO. II)

THIS DOCUMENT RELATES TO:
Civil Action No.: 2:17-cv-06124
FREDDY BALES, Plaintiff
VS
ASTRAZENECA PHARMACEUTICALS LP, et al., Defendants

Civil Action No.: 2:17-cv-02475
DAVID FOSTER, Plaintiff
VS
ASTRAZENECA PHARMACEUTICALS LP, et al., Defendants

Civil Action No.: 2:18-cv-03159
STEVE KERSCH, Plaintiff
VS
ASTRAZENECA PHARMACEUTICALS LP, et al., Defendants

Civil Action No.: 2:17-cv-00212
KIMBERLY LEE, Plaintiff
VS
ASTRAZENECA PHARMACEUTICALS LP, et al., Defendants

CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER

VOLUME II
GILBERT W. MOECKEL, M.D., PH.D., FASN
July 8, 2021

Civil Action No.: 2:17-cv-13727

DIANE NELSON,
Plaintiff

VS

ASTRAZENECA PHARMACEUTICALS LP, et al.,
Defendants

Civil Action No.: 2:19-cv-00850

JAMES RIEDER,
Plaintiff

VS

ASTRAZENECA PHARMACEUTICALS LP, et al.,
Defendants

CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER

VOLUME II

Continuation of the videotaped deposition of GILBERT W. MOECKEL, M.D., PH.D., FASN taken via Zoom videoconference before Clifford Edwards, Certified Shorthand Reporter and Notary Public, on July 8, 2021, at 11:05 a.m.

GOLKOW LITIGATION SERVICES
877.370.3377 ph | 917.591.5672 fax
deps@golkow.com

A P P E A R A N C E S: (all via videoconference)
ON BEHALF OF THE PLAINTIFFS:
PAUL PENNOCK, ESQ.
MORGAN & MORGAN
90 Broad Street, Suite 1011
Brooklyn, NY 10004
ppennock@forthepeople.com
BESS DeVAUGHN, ESQ.
DOUGLAS & LONDON, P.C.
59 Maiden Lane, 6th Floor
New York, NY 10038
bdevaughn@douglasandlondon.com
JONATHAN M. SEDGH, ESQ.
MORGAN & MORGAN
90 Broad Street, Suite 1011
Brooklyn, NY 10004
jsedgh@forthepeople.com
SERENA ROSAS, ESQ.
NAPOLI SHKOLNIK, PLLC
270 Muñoz Rivera Avenue, Suite 201
Hato Rey, Puerto Rico 00918
(833) 271-4502

ON BEHALF OF THE DEFENDANT ASTRAZENECA:
KATHERINE D. ALTHOFF, ESQ.
ICE MILLER LLP
One American Square, Suite 2900
Indianapolis, IN 46282-0200
katherine.althoff@icemiller.com
OLGA VOINAREVICH, ESQ.
ICE MILLER LLP
One American Square, Suite 2900
Indianapolis, IN 46282-0200
olga.voinarevich@icemiller.com

A P P E A R A N C E S: (all via videoconference)

ON BEHALF OF THE DEFENDANT TAKEDA:

JAMES W. MIZGALA, ESQ.
TUCKER ELLIS LLP
233 South Wacker Drive, Suite 6950
Chicago, Illinois 60606
james.mizgala@tuckerellis.com

ANDREA M. GLINKA PRZYBYSZ, ESQ.
TUCKER ELLIS LLP
233 South Wacker Drive, Suite 6950
Chicago, Illinois 60606
andrea.przybysz@tuckerellis.com

ALSO PRESENT:

EMILY SY, ESQ., TAKEDA
JEFF FLEMING, VIDEOGRAPHER/EXHIBIT TECHNICIAN
LEO RAKITIN, ESQ, ASTRAZENECA

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(continued)

THE VIDEOGRAPHER: We are now on the record. The date is July 8, 2021. The time is 11:05 a.m.

This is the continuation of the deposition of Dr. Gilbert Moeckel.

CROSS-EXAMINATION

BY MR. MIZGALA:

Q Good morning, Doctor. How are you?

A Good morning. I'm doing fine. Thank you.

Q Okay. Good.

My name is James Mizgala. I'm -- I'm here on behalf of Takeda. I'm going to ask you some questions about the other report you wrote today.

A Right.

Q Just to remind you, you -- you are still under oath, sir; okay?

A Yes. I understand.

MR. MIZGALA: Okay. So let's pull up Exhibit 13.

(Whereupon, Exhibit No. 13, Expert Opinion Report, Gilbert W. Moeckel M.D., Ph.D., FASN, dated May 20, 2021, was marked for identification.)

BY MR. MIZGALA:

Q Doctor, can you identify Exhibit 13 for the record, please?

A Yes. This is my expert witness report on the Takeda studies.

Q On the third page, it says it was prepared for Bess DeVaughn; is that correct?

A Yes, that's correct.

Q How do you know Ms. DeVaughn?

A Ms. DeVaughn is a member of the plaintiff legal team.

Q Was she the one who contacted you about consulting in the first instance for the plaintiffs?

A Yes.

Q Okay. Do you know how she got your name?

A I don't know.

Q Okay. Did you reach out to her at all?

A No.

Q Have -- have you ever consulted with Ms. DeVaughn or the law firm of Douglas & London previously?

A No.

Q Let's go to page 37, please.

A Uh-huh.

Q Is that your signature, sir?

A One moment, please.

Yes, it is.

Q Okay. And this is dated May 20th of 2021; correct?

A That is correct, yes.

Q Have you -- did you review your report in preparation for this deposition?

A Yes, I did.

Q Okay. Is there anything in your report that needs to be changed?

A No.

MR. PENNOCK: Note my objection.

Go ahead.

A No.

BY MR. MIZGALA:

Q Okay. And, sir, does your report reflect or contain all of the opinions that you intend to offer at trial in this case?

A Yes.
Q I know you're reserving the right to supplement, but at this time, do you have any plans to supplement your report?
A No.
Q Okay.
MR. MIZGALA: Let's turn to page 5, please. Page 5.
There you go.
BY MR. MIZGALA:
Q Okay. Doctor, this section is titled "Expert Approach and Methodological Assessment."
Right?
A Yes.
Q You spent a lot of time talking with Ms. Althoff yesterday about your methodology or approach.
Was there anything different about how you approached your review of the Takeda images versus your review of the AstraZeneca images?
A No.
MR. PENNOCK: Objection.
A No.
BY MR. MIZGALA:
Q You also -- on the first line, it says,

"Similar to my approach regarding the non-clinical studies sponsored by AstraZeneca and Pfizer Wyeth."

What studies -- nonclinical studies did you review with respect to Pfizer?

A I was giving -- I was given studies that were conducted by Pfizer Wyeth.

Q Relating to what drug?

A To proton-pump inhibitors.

Q Was that to pantoprazole?

A I believe -- I believe so. I do not remember exactly.

Q Okay. But you haven't written a report with respect to your review of those studies; is that correct?

A I have not written a separate report on those studies.

Q Okay. You say here first you "sought to obtain information about nonclinical testing programs performed by Takeda."

Correct?

A Correct.

Q And it says you "considered and relied on defendant-manufacturer, regulatory submissions, consisting of, among other things, non-clinical

trial indices and study reports."

Right?

A Yes.

Q Okay. Any -- any other regulatory submissions beyond nonclinical trial indices and study reports did you consider for your opinions?

A No.

Q Did you review any of the FDA reviews -- the pharmacology reviews of Takeda's nonclinical studies?

A One moment.

I believe not.

Q Okay. Did you ask for those?

A I believe not.

Q You know those are publicly available online?

A I was not aware.

Q Okay. And it says you also "considered documents produced as part of the litigation process, deposition testimony, and other company-specific documents."

Correct?

A Yes.

Q Okay.

MR. MIZGALA: Let's go, Jeff, to

the document. And this is going to be Exhibit 14. It's Dr. Gilbert Moeckel, PPI MDL 5.20.21 Expert Report - Exhibit B, Materials Considered.

(Whereupon, Exhibit No. 14, Materials Considered by Expert Dr. Gilbert W. Moeckel, was marked for identification.)

MR. MIZGALA: Excellent.

BY MR. MIZGALA:

Q Okay. And, Doctor, this is your materials considered list; is that correct?

A That is correct.

Q Okay. The first thing listed are a couple depositions for David Crawford and Stuart Levin.

Did you read those depositions?

A I read the deposition on Stuart Levin -- by Stuart Levin.

Q The entire deposition?

A I believe so, yes.

Q Okay. And did you get all the exhibits to that deposition?

A I believe so.

Q Okay. And so you did not read

Dr. Crawford's deposition; is that correct?

A That is correct.

Q Okay. The labels for Dexilant, Prevacid, did you review all those?

A Yes, I reviewed them.

Q Okay. Then there's a section -- it says "Designated Confidential Documents Produced by Takeda." And there's 37 of them.

Did you review all of those?

A Yes.

Q Okay. And what are those -- what was in those documents, sir?

A I don't remember everything off the top of my head.

Q Okay. How long did it take you to review those 37 documents?

A A very long time. I do not have exact hours off the top --

Q Okay. And then --

A -- off the top of my head.

Q Okay. Then there's a list of 54. And it says "Takeda Conducted Non-Clinical and Clinical Trials of Prevacid and Dexilant."

Did you review any clinical trials, sir?

A I -- I did not review clinical trials, no.

Q Okay. So just -- just 54 nonclinical trials; is that right?

A Yes.

Q And how long did that take?

A Many hours. I do not know off the top of my head how many exactly.

Q Okay. On page 6, there's a -- a -- this literature list that goes all the way to page 29 -- so 23 pages of literature -- did you review all of those articles, sir?

A Can you repeat that question again?

Q Yeah.

You got -- you got 23 pages of literature here. Did you review -- did you review all -- all of those articles?

A One moment, please.

As far as I remember, I reviewed most of these articles, especially those articles that were pertaining to animal studies and toxic mechanisms of PPI, but I also reviewed a large number of clinical papers.

Q Okay. Finally, on -- on the very -- the -- the penultimate page, there's a category of

other documents.

Did you review all of those, sir?

A Let me quickly look at them. One moment, please.

I reviewed most of these.

Q Okay. The FDA documents, the materials listed, the first several there, summary review, medical review, postmarketing safety review, transcript from the advisory committee --

A Uh-huh.

Q -- summary meeting, meeting summary minutes, citizen petition, did any of those contain any discussion of animal studies and the effects of PPIs on the kidneys of animals?

A Just from the title, I do not remember. I would need to actually see those reports to remind myself whether they contained material.

Q Okay. And you didn't cite any of those as references for your report; correct?

A That is correct, yeah.

Q Doctor, you reviewed Dr. Levin's deposition; right?

A Yes.

Q Okay. Do you know Dr. -- who Dr. Levin is?

A I -- I have not seen his CV, but I know that he is a -- an expert, I believe, in pharmaceutical animal studies.

Q Okay. You've never met Dr. Levin; is that correct?

A That is right.

Q Okay. Do you know anything -- he's a -- he's a DVM.

Do you know anything about his reputation in the field?

A I think he has a solid reputation, but I do not know specifics about his reputation.

Q Okay. You -- you also reviewed his notes from his review of Takeda's preclinical studies; correct?

A Correct.

Q Okay.

MR. MIZGALA: Let's pull that up, Jeff. It's Levin's notes on lanso and dexolanso.

You're good.

BY MR. MIZGALA:

Q Okay. Are these the notes you reviewed, sir?

A Can I look at the entire document,

please?

Q Sure.

MR. MIZGALA: And this is Exhibit 15.

(Whereupon, Exhibit No. 15, Stuart Levin, Notes on Lansoprazole and Dexlansoprazole Nonclinical Toxicity Studies, dated Feb 5, 2019, was marked for identification.)

THE WITNESS: Can you enlarge it, please? Make it bigger?

Yeah. Thank you.

Could you scroll down, please, a little bit?

Scroll down some more, please.

And scroll down, please.

Okay. And some more.

And scroll down, please.

A Uh-huh.

BY MR. MIZGALA:

Q Sir, is this a document you reviewed?

A I believe that I've seen this document at some point, yes.

Q Okay.

MR. MIZGALA: Let's go quickly back to his -- his report, Exhibit 13, page 5. Blow up footnote 3. Okay.

BY MR. MIZGALA:

Q You say, "In addition to the indices and studies themselves, I reviewed the document entitled: 'Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies' authored by Dr. Stuart Levin, Ph.D. dated February 5, 2019."

Okay. Let's go back to Exhibit 15, first page.

This is the document you identified in footnote 3; right, Doctor?

A That's correct.

Q Okay. Let's go to the second page, second paragraph.

Dr. Levin states he reviewed the reports and data from the studies listed in Appendix 1, which, to his knowledge, this included all the studies with treatment periods of 13 weeks (3 months) or longer.

Any issue with that approach, Doctor?

A I -- I have no objection to this approach, no.

Q Okay. And where he says, "In the" -- "In the case of chronic kidney injury and nonclinical toxicity studies, the focus of my investigation, I looked for dose-related increases in the clinical pathology measurements of blood urea nitrogen (BUN) or creatinine as indicators of advanced kidney damage; increased kidney weights; increased incidences of certain histopathology lesions."

Any issue with that approach?

A No. No objection to that approach.

Q Is that similar to what you -- you did when you looked at the studies?

A Yes. I would say that is fairly similar to what I did when I looked at the studies.

Q Okay.

MR. MIZGALA: Let's go back to Exhibit 13, page 5, please.

Up a little higher.

Okay. Right there.

BY MR. MIZGALA:

Q Okay. This paragraph that starts, "As in the case of my approach to the AstraZeneca and Pfizer Wyeth non-clinical studies, after

determining the extent and type of studies performed for each of these products, I determined those studies that would provide the most useful and relevant information for me to form my opinions."

Right?

A Yes.

Q And I believe that yesterday you testified that you reviewed dozens and dozens of preclinical studies; correct?

A Correct.

Q Okay. And when you reviewed those, if you didn't see evidence of impaired renal function, you didn't want to see the slides for those studies; correct?

MR. PENNOCK: Objection.

A It was not based on a single parameter. I would say if the -- the degree of renal function as determined, for instance, by creatinine and BUN values -- although creatinine was rarely used in my experience, it was predominantly BUN values, which are not that sensitive, but when there was -- among other things.

As you know, I looked at a -- a number of parameters as criteria why I selected certain

studies, and one of them certainly would be to look at, for instance, elevated BUN levels as a criterion to select that study, yeah.

BY MR. MIZGALA:

Q Sir, you said yesterday if there was any strong single -- signal of -- of renal injury, then you didn't look at those studies any further; correct?

MR. PENNOCK: Note my objection.

If -- if you want to point him to testimony from yesterday, you're going to need to pull that up and show it to him.

BY MR. MIZGALA:

Q Do you recall that, sir?

MR. PENNOCK: Objection.

A So as I said, the criteria were multiple that I used to select the studies. And I said that yesterday, too.

And when I say, you know, indication of impaired kidney function or kidney lesion, that would mean that I look in the report for parameters that indicate physiological impairment, but, also, in the histological description, evidence of histological injury and pathologic

lesions.

So it was not based on a single parameter or a single entity. It was a holistic approach looking at all the different kinds of evidence that we know about that indicate kidney injury.

BY MR. MIZGALA:

Q And that holistic approach, you -- you mentioned that yesterday. You know, you said when -- when you're -- when you're reviewing human renal biopsies, you -- you need to look at the gestalt.

Do you remember saying that?

MR. PENNOCK: Objection.

A Yes.

BY MR. MIZGALA:

Q Okay. And that's the same thing in these studies; right? You need to look at the gestalt.

You've got to, like, know what's going on with the animals, what -- and you mentioned yesterday feeding can affect things like the -- the renal function in rats, you know, high-protein diets.

So you need to know that; right, sir?

MR. PENNOCK: Objection.

A Yes. You need to know all the different factors and criteria that I used to assess impaired kidney function or kidney injury.

BY MR. MIZGALA:

Q Including species-specific differences for rats, dogs, and mice; right?

A As long as it pertains to kidney pathology.

Q Right.

And -- and there are species-specific differences that pertain to -- to kidney pathology for mice, rats, and dogs; right?

A There are some -- some differences between these species, but overall -- and that's why we use them as research tools and as models -- most aspects of kidney function in these different mammalian species are very similar.

Q Sir, you spent a lot of time yesterday talking about CPN, chronic progressive nephropathy; right?

A Right.

Q Okay. Did -- you're not disputing that CPN exists, are you?

A No, I'm not.

Q Okay. And -- and it's a rat-specific phenomenon; right?
A Yes.
Q Okay. Dogs don't get CPN; right?
A To my knowledge, dogs do not get CPN.
Q Okay. And humans don't get CPN; right?
A Humans do not get what is described in the rat as CPN. So there has to be a distinction here.

Humans do get chronic progressive nephropathy, of course. Hypertension, diabetes, yes, they can, for instance, cause chronic progressive nephropathy. And also, chronic progressive nephropathy can have multiple etiologies.

So it's -- it's not something that is just specific to one disease entity.
Q Okay.
A It's --
Q I'm talking about the pathology that you see in the rats. You don't see that in humans, do you?

MR. PENNOCK: Objection.

A Actually, you do see features described as CPN in the rat in the human, absolutely. You

see glomerulosclerosis, tubular basement membrane thickening, tubular atrophy, all these characteristic findings of CPN, yes, we can see them in the human, absolutely. I see them every day.

BY MR. MIZGALA:

Q And -- and -- and as you noted, you see them secondary to things like diabetes and hypertension; right?

A Well, that cannot be said like this. We do not understand all the different factors, physiological, genetical factors, that actually lead to the features of glomerulosclerosis and tubular basement membrane thickening in humans.

In fact, that is a great area of study at the moment to discover genetic predisposition to these lesions in humans.

Q Sir, have you ever diagnosed on a renal -- human renal biopsy chronic progressive nephropathy?

A Almost every day I diagnose on a human biopsy progression of chronic kidney disease which has many similar features of those described in CPN in the rat.

Q Sir, I want to know: Have you used the

words "chronic progressive nephropathy" on a renal biopsy for a human?

A I may have used it in some of my descriptions and comments of diagnosis in the past. I often comment about progressive chronic nephropathy in humans when I see it, and it's -- it's -- it's often there.

Q Sir, have you ever diagnosed on a human renal biopsy CKD secondary to PPI use?

A I do not remember off the top of my head that I have used this specific diagnosis recently, but when we have the features of progressive chronic nephropathy or progressive chronic kidney disease in a human biopsy, then all these different etiologies that are currently entertained are certainly taken into account in our discussions.

Q So you said, "Recently."

Have you diagnosed anyone with chronic kidney disease secondary to PPI use?

A I -- I do not remember off the top of my head. And that's why I said, "Recently." But if it was within the last year, I would remember. Beyond that, I -- I don't remember. I don't remember all the diagnosis.

I sign out over a thousand kidney biopsies per year. I have signed out nearly 20,000 kidney biopsies in my life. I do not remember all the diagnosis that I've used.

Q Going back to page 5 of your report, toward the bottom of that second paragraph where you say, "I asked to see kidney tissue" -- "kidney tissue from studies of different types and treatment periods to detect whether lesions suggestive of drug toxicity manifested as acute insults and/or chronic lesions."

Right?

A Yes.

Q Okay. So you were expecting to see lesions suggestive of drug -- drug toxicity; right?

MR. PENNOCK: Objection.

A As my selection process indicated, I selected reports where I had either reason to believe there might be a toxic renal pathology lesion because of the description in the report or where I was from the design of the study, interested in seeing kidney tissue in order to evaluate whether there might be pathological lesions present that the investigator might have

missed.
BY MR. MIZGALA:
Q And -- and that second category -- so the first category is you -- you picked out studies where you expected to see something; right? Renal pathology?
MR. PENNOCK: Objection.
A Yes.
BY MR. MIZGALA:
Q Okay. The second category, you said study designs where the -- the reviewer might have missed something.
How did -- explain that to us. How did -- how did you do that? What was it about the study design?
A So for instance, if there was a long-term application of the drug over several months where a lesion could be expected because of the long length of the exposure, but the study report either did not mention that they reviewed kidney section; they did not look at them, or where they just had generic sentences saying, you know, the kidneys look completely normal, then I would want to look at those studies in more depths, and also hopefully slides, to see whether,

you know, there was a lesion or not.

Q Okay. You didn't look at all the studies, though, or you didn't look at slides from all the studies; right?

A So I -- I -- I looked at all the slides of the studies where I received slides. But I want to point out that I only received slides on a small number of studies, certainly not of all the studies that I requested.

Q Okay. Continuing on page 5, you say, "My choice of studies to review for each of the PPI products is based upon my experience and training as a renal pathology" -- "pathologist" -- sorry -- "and kidney disease researcher."

Right?

A Yes.

Q Okay. And then you say, "These studies included, among others, the nonclinical studies submitted to support the clinical use of PPIs, as identified in regulatory submissions, where the kidneys of the test animals had been harvested and examined."

Right?

A So just point me out where -- where is it exactly? Can you show me that on the screen?

Q Right. "These studies" -- see it?
A Okay. Yes.
Q Okay. So you say "the nonclinical studies submitted to support the clinical use of PPIs." And that means the studies that were submitted to the FDA for drug approval; right?
A Yes.
Q Okay. And you say, "These studies included, among others."
What other studies did you look at, if any?
A I do not remember off the top of my head.
Q Okay. I don't -- in your -- in -- in your report and in your materials considered, I don't see any other nonclinical studies other than those that were submitted by Takeda for drug approval.
So the -- are there any other studies?
A I don't remember off the top of my head.
Q Okay. And you say farther down, "I analyzed studies performed on both young and old animals of different species to discern whether renal effects were consistent (or not) across

different age groups and different species."

Right?

A Yes.

Q Okay. Why is consistency, or not, across different age groups and different species important?

A So for instance, if you take the lesion of acute tubular injury which I saw in rats and dogs and mice, then it tells me that when, for instance, it is dose-dependent, that that is a strong signal of that drug causing tubular necrosis in the kidney.

Q In those animals; right?

A In those animals, yes.

Q Okay. And -- and you mention dose dependency.

Why is that important?

A Because it shows that with increase of the drug present in the system of the animal, there is an increase in injury. And many drugs have dose-dependent injury effect on respective organs.

So that is a well-known and in the literature described feature to evaluate drug-dependent toxicity.

Q Okay. And if -- and if it's -- if it's not dose-dependent, what does that mean?
A That it is not dose-dependent.
Q Okay. Then -- then you're not suspecting that it's a toxicity from the drug; right?
A No, that is not correct what you just said. Because a drug can do a -- induce a, for instance, hypersensitivity reaction in the setting of acute interstitial nephritis which is not dose-dependent.
Q Okay. What about your tubular injury that you're talking about --
MR. PENNOCK: Objection.
BY MR. MIZGALA:
Q -- not hypersensitivity?
MR. PENNOCK: Objection.
A So acute tubular injury has --
(Whereupon, the court reporter requests clarification.)
MR. MIZGALA: Yeah. I'll just start again.
BY MR. MIZGALA:
Q Dose dependency, you mentioned it's -- for a hypersensitivity reaction, it may not

matter.

But what about what you talked about, what you saw or you say you observed in these studies, the acute tubular injury, how does dose dependency factor in there?

MR. PENNOCK: Objection.

A Acute tubular injury can be caused by a variety of processes that are called organized necrosis or organized cell death or apoptosis.

And we know from brilliant experiments in isolated profuse tubules and in dozens and dozens of animal studies that these organized necrosis and apoptosis processes can be enhanced in a -- in their extent and severity by an increase of the toxic agent that is used to induce these cell death mechanisms.

BY MR. MIZGALA:

Q Doctor, I didn't hear you say organized necrosis or apoptosis when you were describing the pathology you observed yesterday.

Is -- is that -- is that something you observed in the studies -- in -- in the slides that you reviewed?

MR. PENNOCK: Objection to form.

That's a ridiculously butchered

question.

Objection to your testifying as to what was testified to yesterday. If you want to talk about his testimony yesterday, please pull it up. Thank you.

Go ahead.

MR. MIZGALA: Well, I'm talking about what he didn't testify to yesterday, Paul. So just calm down.

BY MR. MIZGALA:

Q Doctor, did you see apoptosis and organized necrosis in the images of the Takeda pathology that you reviewed?

MR. PENNOCK: That's a good question in terms of form. I'm going to not object to that question. It's not butchered like the other one.

A So obviously, you cannot make by light microscopy the diagnosis of apoptosis versus organized necrosis.

What I saw in the light microscopic examination, which is what the light microscopy allows you to do, you can identify features of tubular injury such as basil- -- a -- a loss of

brush border, swelling of the cell, nuclear drop-out, sloughing off of the tubular epithelial cells. All of these are the light microscopy features of acute tubular injury.

And on the molecular level, these injuries are caused by, among other things, mechanisms of organized necrosis and apoptosis.

BY MR. MIZGALA:

Q Okay. So based upon the images you received, you were not able to see organized necrosis and apoptosis?

A I cannot differentiate between the two. I could not tell you which one at that time point was present, but I can tell you that certainly one or several of these mechanisms were -- were present.

Q And that's based upon the histopathological features that you could see; right?

A Yes.

Q So you're extrapolating backwards; right?

MR. PENNOCK: Objection.

A We know that acute tubular injury is caused by a variety of mechanisms that include

apoptosis and the different forms of organized necrosis, which, by the way, I did mention yesterday, such as ferroptosis, pyroptosis, necroptosis, which I mentioned yesterday.

So we know that these mechanisms are the mechanisms that are usually involved in acute tubular injury.

BY MR. MIZGALA:

Q Okay. And -- and I remember you mentioning those specific mechanisms. I was just asking you if you actually observed them in the slides.

MR. PENNOCK: Objection. There's no question.

A It is not -- it is not possible to observe them by light microscopic inspection.

BY MR. MIZGALA:

Q Okay. And you mentioned a variety of different potential mechanisms that could be causing acute tubular injury; correct?

A Yes.

Q Okay. Do you know which one was at play in the rats that -- from the -- from the images you observed?

MR. PENNOCK: Objection.

A I -- are you asking me to tell you which type of organized necrosis was present?

BY MR. MIZGALA:

Q Yeah.

A The tubular injury of the rats?

Q Yeah.

Can you do that?

A No. By light microscopy, you cannot tell that.

Q Okay. You can't do that for the mice or the dogs either; right?

A Right.

Q Okay. Bottom of page 5 -- and this is going to -- it goes over. It says "both high dose studies as well as those in which the dose" --

MR. MIZGALA: Stop right there.

Stop. Go back. There. Good.

BY MR. MIZGALA:

Q -- "in which doses administered to test animals more closely approximated therapeutic doses in marketed PPI products for...humans."

Right?

A Right.

Q Okay. What is the dose of lansoprazole in rats in milligrams per kilogram per day that

most closely approximates the therapeutic dose in -- in humans?

A So let me just quickly review.

Q What are you reviewing, Doctor?

A Oh, I'm just reviewing the different dosages that were used.

And I -- I -- I just want to say as a qualifier that I am not an internist. So I'm not prescribing these drugs to humans.

But it -- it is my understanding that concentrations that are in the realm of 1.5 to about 15 milligrams per kilogram per day is in the realm of the drug concentration's use in patients.

Q You said 1.5 to what?

A To 15 milligrams per kilogram per day.

Q Okay. That's a tenfold difference; right?

A Right.

Q So you're saying -- that doesn't make sense, Doctor, does it?

A Actually, it does -- it does make perfect sense.

What I'm saying is -- and I want to point out again I'm not an internist who prescribes these drugs to patients, but from my

review of the literature, I understand that concentrations that are in between 1.5 milligram per kilogram per day to -- maximum up to 15 milligrams per kilogram per day are within the range that is the prescribed dose in patients.

Q Okay. That 1.5 to 15 milligrams per kilogram per day, are -- is that -- are you talking about a dose in a rat? Are you talking about a dose in a human?

A I believe that that concentration would be in the range of what is given to humans. Although, I want to say that I do not prescribe this drug to patients.

Q Okay. What -- but you talk about doses administered to test animals that most -- more closely approximated therapeutic doses.

What -- I'm just trying to understand what dose that is in a rat in a milligram per kilogram per day that more closely approximate -- approximates what's happening in humans?

A Well, we have to ask the rat whether it suffers from reflux disease.

But what I meant with this sentence was that that concentration range is approaching more closely the therapeutic dosage range that is used

for PPIs in humans.

Q Okay. And I -- I appreciate that.

And what is the dose you would give to a rat to approximate the range that you would see -- expect in humans?

MR. PENNOCK: Objection. Asked and answered.

Go ahead.

A So --

BY MR. MIZGALA:

Q Do you know, Doctor?

MR. PENNOCK: Objection.

Are you withdrawing the last question?

MR. MIZGALA: No. I'm following up on it.

BY MR. MIZGALA:

Q Doctor, do you know what it is?

A I don't treat --

MR. PENNOCK: Objection. Form.

A I don't treat rats for gastric reflux or that kind of disease. So I -- sorry. I cannot interview my rats whether, you know, that drug range helps them better than not.

So I -- I -- I think your question is

nonsensical to me, but --

BY MR. MIZGALA:

Q Well, that -- you -- okay.

If you were -- if -- you're a scientist; right, Doctor?

A Right.

Q If you're not comparing the -- the -- the level of dose you're giving to the rats to what you would expect to use -- see in humans, how can you make a valid comparison?

MR. PENNOCK: Objection.

A Well, I think the thing -- as I said before, the -- the dosage range that I mentioned before is more comparable to what the dosage range is that is given by internists to humans. So this is all I'm saying.

Whether it has the -- whether it's the optimal dose to treat a rat for peptic ulcer disease, I don't know. That's a question for a veterinarian.

BY MR. MIZGALA:

Q Doctor, I'm not talking about treating the rat for GERD or peptic ulcer disease.

I'm talking about: How do you compare the levels that -- of -- of lansoprazole on a

milligram per-kilogram per-day basis between a rat and a human?

You -- you know people do this all the time; right?

MR. PENNOCK: Objection. Form.

A Well, all I can tell you is that the dosage in humans can be expressed in milligrams per kilograms per day. And it is my understanding, although I'm not an internist, that these dosages that I mentioned earlier are in the same concentration rate if you measured them in the plasma of humans as it's used to treat humans for peptic ulcer disease.

So basically, I'm saying that the dosages that are normalized by the kilogram weight would be comparable.

BY MR. MIZGALA:

Q Okay. Some of the rat studies, they gave the rats 5 milligrams per kilogram per day; right?

A Yes.

Q Okay. And there were studies where they gave them 300 milligrams per kilogram per day; right?

A Yeah. And even more. I think I

remember 2,400 milligrams per kilograms per day.

Q Okay. Big difference between those doses; right, Doctor?

A Yes.

Q Do you know how the 5 milligram per kilogram per day compares to what a human would experience?

A As I said, I'm not an internist who treats patients with these drugs. That -- that is not my job.

So all I can tell you is that from my review of the literature, I have the impression that 5 milligrams per kilograms per day would be a dose that could be used in humans.

Q 300 milligrams per kilogram per day would be a supratherapeutic dose then; correct?

A I -- without being an expert in this, I would assume this, yes.

Q Okay. Let's go down a little farther on page 6. It said --

MR. MIZGALA: Right there.

BY MR. MIZGALA:

Q You say, "I reviewed the reports described above and identified lesions in the kidney that occurred in greater numbers and in

greater degrees of severity in the dosed animals versus the controls."

Right?

A Let me quickly read where that is.

Q That first paragraph.

A Uh-huh.

Yes.

Q Okay. So greater numbers and in greater degrees of severity the -- the lesions were in dosed animals than they were in controls; right?

A Yes.

Q Okay. And when you say "reports" there, that -- you're -- you're talking about the nonclinical studies you reviewed; right?

A Yes.

Q The ones that were submitted to the FDA as part of the drug approval process; right?

A Yes.

Q Okay. And the -- and the information -- oh.

The information about the lesions in the kidney that occurred in greater number and in greater degrees of severity, that was in those reports that were submitted; right?

A Yes.

Q Okay. And then you say that -- you noted that "the reviewing pathologist typically diagnosed these lesions as species-specific, age-related changes that are irrelevant in humans, with, at times, only limited descriptions of the tissues examined."

Right?

A Yes.

Q And those diagnoses were also included in the reports you reviewed; right?

A Yes.

Q Okay. So then you say, "Therefore, I asked to examine the harvested renal tissues, to the extent available, in the form of slides or otherwise (preserved renal/kidney tissue; renal/kidney histopathology slides microscopic photographs or other contemporaneous color" -- "color imaging) to determine possible etiologies for the pathological descriptions contained within the study reports you reviewed for each of the aforesaid products."

Right?

A Yes.

Q Okay. So prior to receiving the

slides -- or you didn't receive slides on the Takeda -- in -- for Takeda; right? You received images?

A Yeah. So they are called virtual slides.

Q Okay. And that's what you also received for -- for the AZ pathology, too; right?

A Yes.

Q Okay. And those virtual slides, you decided which virtual slides you wanted to see after reviewing the clinical study -- or the preclinical study reports; right?

MR. PENNOCK: Note my -- note my objection to the use of virtual slides.

A So I requested the virtual slides or the images from Takeda. I received flash drives with 7,000 images. And what I did is that I reviewed each file. These slides come in electronic files. And I then discerned from my inspection which I wanted to review more closely.

BY MR. MIZGALA:

Q But my question, sir, was that: Before you ever read -- reviewed those slides, you had already reviewed the preclinical study reports and decided which slides you wanted to review; right?

A Well, I did not decide which slide I want to review from the report. From the report, I just decided I want to see the slides on this study.

Q Right.

A I did not determine from reading the report that that slide -- specific slide I want to look at.

Q So you decided which sets of slides you wanted to review after reviewing the study reports?

A No.

MR. PENNOCK: Objection.

A No. I decided to ask for all available kidney slides on a study of interest.

BY MR. MIZGALA:

Q Okay. And how do you define the study of interest?

A I told you many times that I review the study. I decided, based on the design of the study, the length of the study, the dosage of the drug used, the animal species, the pathologic description by the investigators, which study I wanted to look at.

Q Okay. And yesterday you said when you

reviewed the AZ slides, you weren't blinded to the treatment group of the animal that you were reviewing; correct?

A Can you repeat this? You broke up acoustically.

Q Yeah.

Yesterday when you talked about reviewing the AZ slides, you said you weren't blinded to the treatment group of the animal?

MR. PENNOCK: Objection.

BY MR. MIZGALA:

Q You were reviewing; right?

MR. PENNOCK: Objection.

Show him the testimony.

A That is right.

BY MR. MIZGALA:

Q Were you -- were you blinded to the -- to the Takeda slide treatment group?

A No.

Q Okay.

MR. MIZGALA: Okay. Let's go down a little farther. Okay.

BY MR. MIZGALA:

Q And you said this: You "received 3 external hard drives containing over 7,000

digitalized images of kidney tissue sections from a variety of experimental animals from 20 preclinical studies."

Right?

A Right.

Q Okay. And, Doctor --

MR. MIZGALA: Let's go down to footnote 4.

BY MR. MIZGALA:

Q I want -- you say you didn't get images for this one study, A-29439, but I looked at the hard drives that I got, which were supposed to be the -- the same as yours, and A-29-439 is on the label of one of the hard drives, but when you -- when you pull up the -- the files from the study, it's not identified with A-29-439. It's identified with A-86-3109, which is also on the label.

So I think -- I want you to check to see -- you know, you don't have to do it now, but I think you got those images. I just don't think it was identified as A-29-439; okay?

MR. PENNOCK: Objection to the testimony by counsel.

MR. MIZGALA: I'm not -- I'm just

trying to clarify.

Okay. Let's go back up a little, please.

Stop.

BY MR. MIZGALA:

Q Okay. Doctor, you said -- okay. Well, you say, "Using a digital slide reader software."

What -- what slide reader software did you use.

A It's called Qpath.

Q Q --

A Path.

Q Path.

Is there a hyphen in there, or no?

A No.

Q Okay. And -- and you say you reviewed each image; right?

A Yes.

Q Okay. So all 7,000; is that right?

A Yes.

Q Okay. And then you said, based upon that review, you looked at some more closely; is that right?

A Yes.

Q Okay. And then it says "noted the

pathological findings."

What does that mean?

A So I reviewed the slides, and when I identified an area of injury, of a pathological lesion, then I would go high power, which you can do -- do on these virtual slides, and looked very closely.

And if I had the impression that that is a pathological lesion of significance, that's when I took an image.

Q Okay. So when you say that -- you say you noted the pathological findings, you're -- you weren't actually writing out notes?

A No. I -- I looked at the images. And then by visual identification, I see a lesion or not, just like I do every day with kidney biopsy.

Q Okay. Well -- and -- and when you read a kidney biopsy, you actually dictate a note; right? A report?

A Yeah. Later on, when I'm done, yes.

Q Okay. You didn't do that for each one of these images; correct?

A Correct.

Q Okay. So the -- the screen shots you created of the histopathic- -- histopathological

lesions appearing in the images, those are what you included in your report; right?

A Yes.

Q Okay. Are there any screen shots that -- of the Takeda's images that you did not include in your report?

A No.

Q Okay. So they're all in here?

A Yes.

Q Okay. And the -- like you said, this is what you found to be of interest demonstrating the lesions you were observing; correct?

A Yes.

Q Okay. And -- and you say right there, "Below is a discussion of the studies for which I received pathology slides that I consider to be most relevant to my opinion that PPIs cause tubular injury."

Correct?

A Correct. Yes.

Q Okay. You also say, "A brief discussion of other non-clinical studies for which I received pathology images can be found by individual study number in Appendix A attached to this report."

Correct?

A Yes.

Q Okay. So the studies that are listed in Appendix A, are those ones that you do not consider to be most relevant to your opinion that PPIs cause tubular injury?

A Let me quickly review my Appendix A. One moment.

Q Let's -- let's go to that. It's on page -- let's see -- 39.

A Uh-huh.

Can you repeat your question, please?

Q Yeah.

So you -- you said -- you say -- after talking about your review of the images, you said, "Below is a discussion of the studies for which I received pathology slides that I consider to be most relevant to my opinion that PPIs cause tubular injury."

And then you added, "A brief discussion of other non-clinical studies for which I received pathology images can be found in individual" -- "by individual study number in Appendix A attached to this report."

My question was: Are the studies

listed in Appendix A ones you considered not to be the most relevant to your opinion that PPIs cause tubular injury?

A I want to say I still consider them very relevant, maybe not most relevant.

Q Okay. Okay. You have a -- a -- in Appendix A, you have -- you first talk about the rat; right?

A Yes.

Q And then you say "Summary of observations" -- or "Less than one month."

"Summary of observations: occasional animals show peri-tubular capillary congestion and acute tubular injury" in that -- two animals; correct?

A Yes.

Q Okay. Do you know whether those were dosed or control animals?

A I believe they were dosed.

Q Okay. And then you identify the study, TAP-TA97-832: "Oral Gavage Toxicity Study with Lansoprazole in Preadolescent Rats."

Correct?

A Yes.

Q Okay. So I take it, Doctor, you would

agree there's no dose-dependent effect in that study; right?

A I -- I cannot confirm that unless I would go back to the study and look exactly at these animals and see what dosage they got and what the relationship of the dosage is.

Q And did you -- did --

A So off the top of my head, I cannot tell you that.

Q Okay. Did you actually do that on any study, Doctor?

A What -- do what?

Q Do a -- do a -- basically a dose-response analysis.

A I looked at the different groups, dosage groups, and I reviewed respective slides from different dosage groups. And if I saw an increase in the lesion with an increase in dosage, then I would say that that is a lesion that is increasing with dosage.

Q Did you do that for all the animals in -- in a -- in -- let's pick out Study A. And you've got, let's say, four different groups: A control and then three different dose groups.

Did you actually go through that study

and say, okay, I'm going to look at all the control animals and identify what the level of -- what the level of pathology was, dose group one, two, three, do the same thing, and do an analysis across all those dose groups?

MR. PENNOCK: Objection.

A Yes. That's what I did.

BY MR. MIZGALA:

Q Okay. And -- and where is that? Where is that analysis?

A Can you repeat and say more precisely what you mean, where that is?

Q Yeah. Where -- do you have a piece of paper that shows that you did that or --

A No. This is how I reviewed all the slides. I said earlier that I looked at all the control and dose animals. And then when I saw a lesion, I took note of it and took a picture if I think it was relevant.

Q But taking note of it means that you -- you -- you know, it -- it caught your attention.

It doesn't mean you actually took notes on a piece of paper; right?

A A mental note. A mental note.

Q Okay. So your dose-response analysis

was based upon your mental notes; is that correct?

A Yes.

Q Okay. Going back to Appendix A, "Longer than 1 year," you have for the rats, "Summary of observations: severe extensive injury with acute tubular injury; nuclear drop out; congestion; cytoplasmic vacuoles; focal cortical necrosis; congestion, extensive basophilia; casts; focal calcifications; and [sic] lymphocytotic infiltrate."

And then you identify a study; correct?

A Yes.

Q Were -- those observations, can -- can -- do you -- can you tell us, were -- were they seen in the control group, in the dose groups, across the different groups? They seen in all -- in all animals?

What are they -- what do they pertain to?

A To dose animals?

Q Just dosed animals.

A Yes.

Q Okay. Okay. In the mouse, you have "Longer than 1 year."

"Summary of observations: While I did

observe evidence of tubular injury in some control animals, the injury in control animals was very mild and very focal."

Right?

A Yes.

Q Okay. So you saw pathology, tubular injury in some control animals; right?

A In -- in the -- in this one mouse study, yes.

Q Okay. And -- and control animals don't receive drug -- study drug; right?

A They should not receive study drug. They might receive vehicle. And I do not remember exactly what kind of vehicle these mice might have received.

Q Okay. If they are not receiving drug -- study drug, then the study drug can't be causing the tubular -- tubular injury that you observed; correct?

A Correct.

Q You also noticed amyloid deposits; right?

A Yes.

Q What are -- what are amyloid deposits, Doctor?

A Amyloid deposits are deposit of a certain pathologic protein that is in the beta-pleated sheet formation and, therefore, causes abnormal accumulation, specifically in vascular and capillary structures such as the glomerulus.

In fact, in the kidney, the glomerulus is one of the most common locations of abnormal amyloid protein deposition.

Q And -- and -- and it -- and it's called amyloidosis; correct?

A If it is systemic, and most of amyloidosis diseases are systemic diseases, it's called amyloidosis.

Q Okay. And -- and that occurs spontaneously in mice; right?

A I -- to be honest with you, I am not an expert in this. I believe I have seen comments in literature that I reviewed that amyloid may be seen spontaneously in mice.

But, again, I would need to review and study that to confirm for sure.

Q Okay. But amyloid deposits in the kidney can cause renal injury; correct?

A Yes.

Q Okay. And the last one, Doctor, dog, "Less than one month," your summary of observations is "Minimal injury in most kidney sections of dosed groups."

Right?

A Yes.

Q Okay.

MR. MIZGALA: Do you want to take a short break or do you want the keep going? It's up to you.

THE WITNESS: Yes, I would like maybe a five-minute break?

MR. MIZGALA: Sure.

THE VIDEOGRAPHER: Off the record 12:20 p.m.

(Whereupon, there was a recess taken from 12:20 p.m. to 12:30 p.m.)

THE VIDEOGRAPHER: On the record 12:30 p.m.

BY MR. MIZGALA:

Q Let's go back to Exhibit, the report, 13.

MR. MIZGALA: Why did you stop my video? It says the host --

THE VIDEOGRAPHER: Yeah. I -- I meant to stop mine. I'm sorry. I think your picture moved right when I clicked on it some -- for some reason.

There you go.

MR. MIZGALA: I thought Paul was at work.

Hi, Bess.

MS. DeVAUGHN: Hi.

BY MR. MIZGALA:

Q Let's go -- let's jump back -- I want to ask you a question here.

On page 6 -- okay.

MR. MIZGALA: Blow up the lower part of that. A little farther down.

Yeah. There you go.

BY MR. MIZGALA:

Q Doctor, the -- the sentence that says, "Below is a discussion of the studies for which I received pathology slides that I considered to be most relevant to my opinion that PPIs cause tubular injury," you're talking about causing tubular injury in animals; correct?

A Correct.

Q Okay. At the bottom here, it says, "In

Appendix B (also attached to this report), I discuss other non-clinical studies by individual study" --

MR. MIZGALA: Go down a little bit, please.

Stop.

BY MR. MIZGALA:

Q -- "number for which I...requested pathology slides, but these other slides were not...available to me."

Right?

A Yes.

Q Okay.

MR. MIZGALA: Let's jump to page 41, please. In Appendix B; right?

BY MR. MIZGALA:

Q And these are the -- those -- these are the studies you were referring to in your report; right?

A One moment, please. I'm sorry. I just want to find those in my report real quick.

Yes. That is correct.

Q Okay. I counted 21 studies.

Does that seem right to you?

A Yes.

Q Okay. And there's this column that's on there, the final column. It says "Relevant Excerpted Kidney Pathology Findings as Described in Study Reports."

Right?

A Right. Yes.

Q Okay. So you took that -- the information in that column is directly from the study reports that were submitted to the FDA as part of the drug approval process; right?

A Right.

Q Okay.

MR. MIZGALA: Let's go back to page 6. Actually, page 7.

BY MR. MIZGALA:

Q Okay. Doctor, you talk about reviewing "a 1994 summary report entitled A-29-2116: Preclinical Expert Report Lansoprazole (Long-Term Maintenance Treatment) authored by Takeda Consultant in Toxicology Dr. Ralph Heywood, Ph.D."

Correct?

A Yes.

Q Okay. Do you know who Dr. Heywood is or was?

A Yeah. I believe he is one of the

scientists involved in the Takeda studies.

Q Do you know anything about his reputation in toxicology?

A I -- I have not studied his CV. I believe that he is a reputable scientist, but I do not know specifics.

Q Okay. You -- you copied some of the language from his report down there.

MR. MIZGALA: Go down to that indented paragraph. Blow that up a little bit. Make it easier to see.

BY MR. MIZGALA:

Q Okay. And it says, "The severity of nephropathy (CPN), a rat specific lesion showed an increase in comparison with controls in both carcinogenicity as [sic] studies with dosing 7 days a week. This was particularly true with respect to the female animals. The nature of the increase was minor as it did not lead to an increase in mortality as a result of renal failure."

That's what you put in your report; right?

A Yes.

Q Okay. And all that is true; right?

A This is what he described or concluded from these studies.

Q Okay. And do you disagree with his conclusion?

A I -- I would not agree with the word that the nature of the increase was minor.

Q Okay. Well, how about the first sentence, would you disagree with anything there?

A No.

Q And the second sentence, that it was particularly true with respect to female animals?

A I do not disagree with that sentence.

Q Okay. So you disagree that the increase was minor.

What -- how would you characterize the increase?

A I believe that in some studies, we saw a significant increase in pathology.

Q Okay. And when you say "significant," can you quantify that in way?

Are you talking about statistically significant or just based upon your impression based upon your review and mental notes?

A With "significant," I mean that the lesion was extensive.

Q Okay. Compared to what you saw in the controls; right?
A Yes.
Q Okay. And, again, that's based upon what you describe as your mental notes; right?
A Yes.
Q Okay.

MR. MIZGALA: Jeff, let's pull up what's marked as A-29 -- A-29-2166. And that'll be the next exhibit.

(Whereupon, Exhibit No. 16, Preclinical Expert Report Lansoprazole, was marked for identification.)

BY MR. MIZGALA:
Q Okay. Doctor, you -- you recognize this as the report by Dr. Heywood? You see up there at the top right "A-29-2116." Right?
A Yes.

MR. MIZGALA: Okay. Let's go to page 18, please. Okay.

When you see "Kidney," blow that up from there down.

No. Back.

You see where it says "Kidney"?

Now go down a little bit.

Right there. Okay.

BY MR. MIZGALA:

Q So you included that first paragraph -- part of that first paragraph; right?

A Yes.

Q Okay. And you did not include the section about mice; right?

A No.

Q And what Dr. Heywood said was: "No kidney lesions were recorded in mice."

Correct?

A Correct.

Q Any basis to disagree with that?

A Are you asking me a question?

Q Yeah.

Any basis to disagree with his conclusion?

A Well, I reviewed my studies for Takeda, and I did see kidney lesions. So I would not agree with this sentence.

Q Okay. And then he provides a comment, "No adverse effects on renal function have been observed in patients treated with lansoprazole,"

citing Colin-Jones, 1993; right?

A That's what he is commenting, yes.

Q Okay. I did not see Colin-Jones in 1993 in your references or in your materials considered.

Have you reviewed that study?

A I do not remember.

Q Okay. So you can't tell me one way or another whether or not it supports the statement that's -- that's there; right?

A Right.

MR. MIZGALA: Let's go to the next page, "Conclusion." Blow up the "Conclusion," the first paragraph of that.

BY MR. MIZGALA:

Q Okay. Doctor, you noted in your report that -- or you noted that this report identified the kidney as a target organ; right?

A Yes.

Q Okay. And -- and that's a target organ based on animal studies; right?

A Yes.

Q Okay. And just because something is a target organ in an animal study doesn't mean it's

going to be a target organ in humans; correct?

A No.

Q No, it's not correct or, no, it is correct?

A No. It is -- basically, if a drug or a compound is targeting the kidney, so the kidney is the target organ, then there's a high probability that it will also be in humans targeting the kidney.

Q High probability doesn't mean it's going to always do it, though; right?

A High probability would mean that, more often than not, with very high probability, it will also affect the kidney in humans.

Q Okay. And the way you find that out is by studying humans; right?

A Well, unfortunately -- or fortunately, I should say, we, you know, do not do these kind of toxicological studies in humans. So that's why we use animal models. But many of our drugs that are very effective in humans are -- have been tested and evaluated and learned about in animal models.

So if you have a drug that in animals shows a affinity to injuring the kidney, you can

expect that there is a high likelihood that it will also affect the kidney in humans.

Q Okay. And you would expect the -- the folks at the FDA would know this, too; right?

MR. PENNOCK: Objection.

A Yes.

BY MR. MIZGALA:

Q Since they're the ones who look at all this information and decide whether or not a drug is -- is safe and effective; right?

MR. PENNOCK: Objection.

A Well, I cannot speak for the FDA. You know, I am a renal pathologist who also does a lot of research with animal experiments. I cannot speak what the FDA does or conclude or anything to that effect.

BY MR. MIZGALA:

Q Okay. And, Doctor, the last sentence of the -- the -- this paragraph -- the first paragraph says, "The findings in the liver and kidney are of minor consequence, occurring at maximal tolerated doses and above, and do not represent a hazard to man."

Any basis to disagree with that?

A Yes, I disagree with that.

Q Okay. What is a maximal tolerated dose?

A A maximum tolerated dose in an animal study is a dose that does not kill the animal.

Q Okay. And how does that compare to the human dose?

A The maximum tolerated dose in a human is very similar. It's a dose that the human can tolerate without having severe organ injury and subsequent death.

Q I'm talking about the maximal tolerated dose compared to the human therapeutic dose.

Do you know how those compare, say, for the rat?

MR. PENNOCK: Objection to form.

A Yeah. I would say that the maximum tolerated dose would be significantly higher than what the expected treatment range concentration of that particular drug is.

BY MR. MIZGALA:

Q Okay. And that's something to take into consideration when you're considering the safety of a drug; right?

A Yes.

MR. MIZGALA: Okay. Let's go back

to his report. Let's go to page 8, please.

Okay. Blow that up a little bit.

Okay. That's good.

BY MR. MIZGALA:

Q Okay. Doctor, we're going to go through the -- the studies you included now in your report, similar to what you did with Ms. Althoff yesterday.

So the first study we're going to talk about is A-29-1977, a "Two-Year Oral Oncogenicity Study in Rats of Lansoprazole."

Right?

A Yes.

Q And what's an oncogenicity study, Doctor?

A This is a study that tests whether the drug causes cancer.

Q Okay. And two years is a lifetime for a rat; correct?

A Yes.

Q Okay. And you note, "Per the 1994 Preclinical Expert Report," FDA requested that TAP do this study; right?

A Yes.

Q And they did it at the maximum tolerated dose; right?
A Yes.
Q Okay. In the next paragraph, you -- you talk about the macroscopic and microscopic findings; correct?
A Yes.
Q Okay. And you -- you quote from the study report; is that right?
A Yes.
Q Okay. So the information in there was information you took from the study report that was submitted to FDA; right?
A Yes.
Q Okay. And they say in the quote that you have here, "The incidence of chronic progressive nephropathy (Table 53.2-12) was increased compared to the Vehicle Control group" -- "Control A group in the 25, 75, and 150 mg/kg/day female rats."
Right?
A Yes.
Q Okay. And -- and you have the table below that you took from the report; right?
A Yes.

Q Okay. And the statement that -- the -- the statement that you quoted is true; correct?

MR. MIZGALA: Go down to the table, please.

A Yes, it is true.

BY MR. MIZGALA:

Q Okay. And the -- this -- this table was included in the study report; is that correct?

A Yes.

Q Okay. And when it says "Vehicle Control A," that group received no lansoprazole; right?

A Could you repeat that question, please?

Q The group that's identified as Vehicle Control A received no lansoprazole; correct?

A Correct.

Q Okay. And yet 44 of those animals were identified as having CPN; correct?

A Correct.

Q Okay. So that -- that -- and the CPN in those 44, that was not due to lansoprazole; correct?

A Correct.

Q Okay. Again, CPN is a spontaneous lesion; right?

A Yes. And I assume that they did this accurately and were actually truly seeing CPN.

Q Okay. Well, Doctor, do you have a table similar to this based upon your observations?

A No, I do not.

Q Okay. And then it says -- or -- or -- and then if you look at the 5-milligram-per-kilogram dose, you've got 46 with CPN; correct?

A Correct.

Q Essentially, the same as the control group; right?

A Similar. Not same. Similar.

Q Right.

Forty-four and forty-six; right?

A Yeah. It's similar.

Q And -- and if you look at the 75 milligrams, you have 65 animals with CPN; correct?

A Yes.

Q And in the 150-milligram, it's 67; right?

A Yes.

Q So, again, you'd say those are similar?

A Those are similar.
Q Okay. And you didn't do a dose-response -- you didn't calculate a dose-response curve for this study; correct?
A No, I did not.
MR. MIZGALA: Okay. Go down -- right there.
BY MR. MIZGALA:
Q You say, "The study authors, citing to Bowman...et al, (1990)," attributed the microscopic renal findings in the females to chronic progressive nephropathy. And you have, "'Chronic progressive nephropathy' as a 'common spontaneous renal lesion in Sprague-Dawley rat,' particularly in males."
Right?
A Right.
Q And that's true; right?
A Yes.
Q Okay. And then you have Dr. Levin quoting -- you're quoting from Dr. Levin's notes, and you have a paragraph here. I'm -- I'm not going to read the whole thing.
Is there anything in that paragraph you disagree with?

A Yeah. I disagree with a lot in this paragraph.

Q Okay. Start at the beginning. Tell me what you disagree with.

A I -- I don't agree that CPN as a spontaneously progressive disease occurs in rats at the age of three months.

Q Okay. Okay. Well, let -- the first sentence, is there anything you disagree with in the first sentence?

A No.

Q Okay. The second sentence, anything you disagree with in there?

A No.

Q Okay. So you -- you disagree that CPN can first be detected around three months of age in -- in -- in rats; correct?

A Correct.

Q Okay. Yesterday you said you can't see it until 18 months; right?

MR. PENNOCK: Objection.

A Correct.

BY MR. MIZGALA:

Q Okay. But you do agree that the incidence of CPN and the severity of CPN increases

with the age of the rat; right?

A Yes.

Q Okay. Okay. So the next sentence, "So it is not surprising that the incidence of this spontaneous disease would be higher in groups that had better survival," do you agree with that or disagree with that?

A I think this is too general. I think that not necessarily all old rats get CPN.

So I think that this is just a semantic assumption that a group that has better survival would show increase in CPN. I think that is not pertinent to the study.

MR. MIZGALA: Can you go up a little bit to the table, please?

Stop.

BY MR. MIZGALA:

Q Okay. Doctor, out of -- let's look at the control.

Out of 70 rats -- the number examined; right?

A Right.

Q -- 44 had CPN; right?

A Right.

Q Okay. So not all, but a pretty --

pretty significant number of the rats got CPN; right?

A Right.

Q And -- and you do know that CPN is strain-specific in rats; right?

A There are strains that have a higher incidence of CPN than others.

MR. MIZGALA: Okay. Let's go down a little bit.

Stop.

BY MR. MIZGALA:

Q And it says, the final sentence, "The severity of CPN in the 150 group was not increased, as might be expected if the test-article caused a direct...on the kidneys" -- "direct effect on the kidneys."

Right?

A I disagree with that sentence.

Q On what basis?

A On the basis that if you look in the table at the 150 group, there are 26 with mild CPN compared -- 26 in the TS group with mild CPN compared to only 4 in the vehicle group. And together you have 43 with mild CPN versus the vehicle group has 28 with mild CPN. I think that

is a significant increase of the incidence of CPN -- mild CPN in these animals.

So just by looking at the total numbers, I don't think that you can redissect the individual pathological signals.

Q And -- and you're getting that just by looking at the table; right, Doctor?

A Yes. I look at the data.

Q Okay. And -- and, again, FDA had this data; right?

MR. PENNOCK: Objection.

A I believe so, yes.

BY MR. MIZGALA:

Q Okay. What about the fact that there's -- there's four severe animals in the control group and none in the 150-milligram group, how does that affect your opinion?

A I think that that is possibly just a statistical evidence in this spontaneously occurring lesion in the control animals.

I don't think that that is as significant as the increase with mild CPN in the hundred and fifty group compared to all other groups. And, you know, I -- this is also a study that did not really test for a full development of

CPN in the animals.

So I think that we have this significant increase in mild CPN in the hundred and fifty group might actually be an important signal that the high concentration of the drug is initiating, at this time point of the age of the rat, this lesion.

Q Doctor, if you compare the 150 to 75, there -- there's really no difference in the severities; correct?

A They're similar.

Q And, in fact, there's -- there's -- there's severe in the 75 and, again, there's no severe in the 150; right?

A Yeah. But there are also eleven moderate in the hundred and fifty and only seven moderate in the seventy-five. I would say that is a significant increase.

Q Okay. And -- and five versus zero, would you say that's a significant increase?

MR. PENNOCK: Objection.

A Well, you know, it seems like, when you look at severe in all groups, there are two to four in all groups. So, no, five is not significant.

BY MR. MIZGALA:

Q No. I'm talking about the 70 -- you made a comparison of the 150 to 75.

A Yes.

Q And you were looking at moderate, and you said it was significant that in the 150, it was 11, and in the moderate, it was only 7.

A Yes.

Q A difference of four. You said that was significant.

A Yes.

Q I'm asking you to do the comparison of 150, zero in severe, to 75, where there's five severe.

That's significant, too; right?

A On the other hand, when you come look at the severe in all other groups, they all have four or so severes. Only in the 150 that you have no severes. So that could be an outlier.

While when you look at the mild, the numbers are -- they're across all the controls and the different concentrations. So I think there the -- or the moderate.

So there the increase, I think, is much -- so that means that that increase is much

more significant than what you have in the severe category.

Q Okay. So a difference of four in moderate is significant, but a difference of five in severe is not? Is that what you're saying?

A No. I think you have to look at all the animals across the different gravity of the lesion and dosage.

And what I'm saying is the fact that under severe CPN, you have no animals listed in the 150, that could be just a random outlier. While when you look at mild and moderate where the numbers are very comparable in the vehicle and 5-milligram groups, once you go to twenty-five, seventy-five, and a hundred and fifty, you see that there is a clearly increase in incidence compared to the vehicle.

So I think that that is much more significant if I look at the data sets compared to this one outlier in severe.

Q Okay. Doctor, did you do any analysis where you controlled for age of the animals?

A In which study?

Q This study.

A In this study?

Q Yeah.
A Can you repeat your questions?
Q Yeah.
Did -- when you were talking about incidence in severity, did you control -- did you do an analysis that controlled for the age of the animals?
A I would not have that data, I believe.
Q You -- you don't know that data is in the study tables that were submitted to FDA?
MR. PENNOCK: Objection.
A I did not do a analysis according to the age.
MR. MIZGALA: Okay. Let's go down --
A I don't -- I don't think that that matters.
BY MR. MIZGALA:
Q Okay. You say you reviewed the images.
MR. MIZGALA: Let's keep going.
Okay. Okay. Stop.
BY MR. MIZGALA:
Q Okay. You say here, "As shown below, and pertinent to my own opinions in this case, the lesions in the control group are less severe in

the [sic] dosed groups."

Okay. Is -- what's that based on? Is that based on the images or did you actually tabulate all that data?

A That is according to the evaluation of the extent and degree of acute tubular injury that I am seeing and the infiltrate and the extent of the pathologic lesion.

Q Okay.

A And you --

Q And --

A You don't need to do -- you don't need to do any kind of quantification. The degree of injury is so much more severe that I think it is striking just from looking at these images.

Q Okay. These images.

But did you -- did you -- did you do -- you didn't do like what you -- we saw in Table 11; right?

A No, I did not.

Q Okay. And when you say -- are you -- okay. And this is for the male animals.

And you didn't include -- include the table for the male animals; right?

A Can you repeat your question?

Q Yeah.
You had -- the table you had above --
A Yeah.
Q -- was for the female animals; right?
(Whereupon, the court reporter requests clarification.)
BY MR. MIZGALA:
Q Female animals.
You didn't include the table -- the similar table for the male animals; right?
A No, I did not.
Q Okay. Your -- your -- your opinion that the lesions in the control group are less severe than in the dose groups, you still saw lesions in the control groups; right?
A Yes. For instance, as I point out in the image with the white arrow, there is lymphocytic infiltrate, which in my opinion is a lesion --
Q Okay.
A -- in the animal.
Q And -- and are you saying that the lesions in the control group of the males and the females are less severe than in the dose groups?
A No. I was -- actually, I believe that

sentence pertains to both male and female.

Q Okay.

MR. MIZGALA: Let's go down a little bit. Right there.

Go back up a little bit so he can see the -- little bit more.

There you go.

BY MR. MIZGALA:

Q Okay. You say you "observed distinct lesions in these animals. A, B and C show inflammatory infiltrate (white arrows)."

Right?

A Yes.

Q Okay. And what is inflammatory infiltrate?

A That is an infiltrate in the interstitium of the kidney that consists predominantly of mononuclear cells, and those are usually lymphocytes, macrophages, a small number of plasma cells.

Q Okay. And what's the significance of that infiltrate?

A It is a sign of inflammation.

Q Where?

A In the tubular interstitial

compartment --

Q Okay.

A -- of the --

Q And that means you could have the inflammation in the tubules; right?

A Right.

Q You could have the inflammation in the interstitium?

A Uh-huh. Yes.

Q Okay. You could have the inflammation in the glomeruli; right?

A No.

Q No?

A No.

Q Why not?

A No. Because the -- the -- the lympho-- the interstitial lymphocytic infiltrate is always indicative of a inflammatory process in the tubular interstitial compartment.

Q Okay. So you're saying it's limited to inflammation -- secondary to inflammation either in the tubules or in the interstitium; right?

A Yes.

Q Okay. And those are two separate anatomic features; right?

A Yes.
Q Okay. And you say there is acute tubular injury in B, C and D, red arrows; right?
A Yes.
Q Okay. And are you saying this is not CPN?
A Yes. This is not CPN.
MR. MIZGALA: Okay. Go farther down. Keep going. Keep going. Keep going.
So -- right there. No. Go just a little farther.
BY MR. MIZGALA:
Q Okay. And -- and the females again, you're observing inflammatory infiltrate and severe acute tubular injury; right?
A Yes.
Q Okay. And, again, you're -- you're -- you're -- you go --
MR. MIZGALA: Go down a little bit.
BY MR. MIZGALA:
Q And right there you say what you have observed is not CPN; right?
A Yes.

MR. MIZGALA: Oh. Oh. Keep going down. Oh. Back up a little bit. Back up.

Okay. Right there.

BY MR. MIZGALA:

Q You say, "However the lesions I observed in the [sic] dosed" -- "in dosed groups do not fit in [sic] with the" -- "do not fit within the CPN definition used by Takeda."

Right?

A Yes.

Q Okay. What is the CPN definition that was used by Takeda?

A So the CPN definition used by Takeda was thickening of the tubular basement membranes, proteinaceous casts, glomerulosclerosis, increase in glomerular basement membrane thickness.

Q And where did you get that definition?

A From the description of the CPN in their studies.

Q Was that description included in this study?

A I would need to go back and look at the study.

Q Okay.

MR. MIZGALA: Okay. Go down a little bit. Stop.

BY MR. MIZGALA:

Q Okay. You say, "What was striking in...review of the kidney tissue sections was a significant increase in extent of tubular injury and inflammatory infiltrate with increased dosage of lansoprazole."

Right?

A Yes.

Q Again, you didn't tabulate your results or generate a dose-response curve; right?

A No.

Q And you say, "That should have raised a concern by the investigators to consider a drug dependent etiology of the tubular injury and the inflammation that is clearly seen on a microscop-- "on microscopic inspection."

Right?

A Yes.

Q Then you say, "This in turn should have prompted the investigator to recommend that further toxicology studies more focused on the kidney itself be conducted."

Right?

A Yes.

Q What would those toxicology studies be?

A Well, those would be studies that use PPIs in different -- normal animals and -- and in animals that have a kidney injury model to see whether the drug would exacerbate the injury.

You could, for instance, use a chronic injury model and see whether the drug exacerbates chronicity in this model or you could use an acute tubular injury model and see whether the drug exacerbates the acute lesion there.

So basically, there are many tools and many species available that can be used to examine in depth, in detail, with much larger numbers of animals over different time spans to assess the effect of acute tubular injury by PPI in rats, mice, dogs, all these different animals.

So those should have been the studies that should have been conducted by Takeda.

Q Okay. And -- and have you ever recommended to a pharmaceutical company that they do such studies?

A I have -- I have never recommended to Takeda or AstraZeneca to do these studies because I was never asked to evaluate these studies by

these pharmaceutical companies.

Q Have you -- not just Takeda or AstraZeneca. Has any pharmaceutical company ever asked you, based upon preliminary data, to -- what studies you would recommend they do in follow-up?

A Yes.

Q On the -- on kidney data?

A Yes.

Q And what was that?

A So I was a consultant for Fleet Pharmaceuticals, and I was asked to conduct animal studies in rats regarding the use of Fleet Phospho-Soda causing acute kidney injury. And I developed a rat model where I tested the effect of high phosphate concentration on kidney injury.

Q Fleet, that -- that's the company that makes enemas; is that right?

A That's right.

Q And what you were looking at was acute phosphate nephropathy; right?

A Yes.

Q Or nephrocalcinosis; right?

A Well, nephrocalcinosis is actually something else. Acute phosphate nephropathy is the right term.

Q Okay. And that's a -- is that a crystal nephropathy?
A Yes.
Q Okay. So you weren't looking at acute tubular injury; right?
A Yes.
Q Yes, you were or, yes, you weren't?
A Yes, I was or, yes, I were.
Q Via -- not a direct effect, but via crystal nephropathy; right?
A Well, a direct effect of the phosphate on kidney injury.
Q Okay. Right.
But you -- you get these crystals that form, and the crystals cause the acute tubular injury; right?
A The phosphate that is used in the enema causes the acute kidney injury.
Q I -- but what about the tubular injury? You said you were looking at tubular injury.
A Yeah. Tubular injury, yes.
Q Okay. But you keep saying acute kidney injury.
A Well, that is the modern term for -- that entails acute tubular injury.

Q The phosphate creates -- causes the creation of crystals, which then causes the acute tubular injury; correct?
A Correct. Yes.
Q Okay. It's not a direct effect on the tubule -- tubule cells; right?
A Well, it's -- it's a toxic effect on the tubule.
Q A different mechanism than what you're proposing or you believe might be going on with PPIs; right?
A I cannot speak to that effect because I think the mechanism -- the molecular mechanism of how PPIs injure the tubular epithelial cell are still enigmatic, in my opinion.
Q In your discussion about the study that we just went through, did you say anything about crystals?
A Can you repeat the question?
Q Yeah.
The study we just went through, you -- you talk about acute tubular injury; right?
A Yes.
Q Did you see any crystals?
A Let me just go back.

So in -- in this study, the -- the Takeda A-29-1977 or TA91-024, I believe I did not see crystals.

Q Okay. Doctor, any evidence that FDA agreed with your conclusion that there should have been further studies more focused on the kidney?

A I cannot speak for the FDA.

Q Okay. The next study.

MR. MIZGALA: Go down a little bit, please.

That's good.

BY MR. MIZGALA:

Q This is A-29-1986, "Two-Year Oral Oncogenicity Study in Mice of Lansoprazole."

Right?

A Right.

Q Okay. And there were only two groups in this study; right? A control group and 600-milligram-per- kilogram-per-day group?

A I believe so, yes.

Q Okay. And there were 70 males and 70 females in each one of those groups; right?

A I believe so, yes.

Q Okay. And -- and you've got a conclusion by Dr. Levin there, which you disagree

with; right?

A Yes, that's right.

Q Okay. And you -- and you disagree with him based upon Table 9 from the study report; right?

MR. PENNOCK: Objection.

A Yes, that's right.

BY MR. MIZGALA:

Q Okay. And, again, that study report was submitted to FDA as part of the drug approval process; right?

MR. PENNOCK: Objection.

A Yes, I believe so.

MR. MIZGALA: Okay. Let's pull up, Jeff, what's marked as -- what is this? -- "A-29-1986 (renal)." Okay.

BY MR. MIZGALA:

Q Okay. And do you see at the top, A-29-1986, "Two-Year Oncogenicity Study in Mice." Right?

A Right.

Q Okay.

MR. MIZGALA: Let's go down. Keep going.

COURT REPORTER: Is this marked as

a new exhibit?

MR. MIZGALA: Yes.

(Whereupon, Exhibit No. 17, Scientific Report No. R&D/93/731 and Table 9, Bates Nos. TAKPPI-INDNDA-01620127 through TAKPPI-INDNDA-01620135, was marked for identification.)

MR. MIZGALA: Keep going.

Okay. Do you have any way to rotate the page?

There we go. Okay.

Blow that up, please. Okay.

BY MR. MIZGALA:

Q Doctor, this is Table 9 from that --

A Uh-huh.

Q -- right?

What --

A Right.

Q What was it about these numbers that cause you to disagree with Dr. Levin?

A So when you look at the "Nephritis, interstitial, chronic" --

Q Right.

A -- you can see that there is a increase

in mild chronic interstitial nephritis in the 600-milligram group. And that was the signal that I wanted to examine.

Q Okay. If we look at those numbers across -- you know, let's -- let's break that down a little bit -- "Nephritis, interstitial, chronic," there's 57 in the -- the control group; right?

A Yup.

Q And 56 in the 600-milligram-per-kilogram- per-day group; right?

A Right.

Q Okay. Trace, there's 37 in -- in the control group; right?

A Right.

Q And 26 in the 600 group?

A Right.

Q Mild, you have 12 in the control and 23 in the 600; right?

A Right.

Q And in moderate, you've got 8 in the control and 7 in the 600; right?

A Right.

Q There's no dose-response relationship there, is there, Doctor?

A Well, there is a significant increase in the mild interstitial chronic nephritis, and that is quite significant. That is 23 versus 12. So you have a doubling of mild chronic interstitial nephritis in the dose group.

I think this is a strong signal and needs to be investigated.

Q Okay. And -- and you got that just by looking at that table; right?

A Absolutely.

MR. PENNOCK: Objection.

BY MR. MIZGALA:

Q What was that, Doctor?

A Yes.

Q Okay. The table that the FDA had; right?

MR. PENNOCK: Objection.

A I believe they had this at some point.

BY MR. MIZGALA:

Q And -- and the -- that -- that chronic interstitial nephritis that was in the control groups -- in the control group, that's not due to lansoprazole; right?

A You know, there are many factors that can induce a chronic interstitial nephritis.

So -- but I would say that it is very likely that it was not induced by omeprazole.

Q No. Lansoprazole.

A Lansoprazole. I'm sorry. I apologize.

Q Right.

A Lansoprazole.

Q The control animals weren't getting any lansoprazole. So the pathology seen in them could not be due to lansoprazole; right?

A Correct. Yes.

Q Okay. That is -- is that the only thing you were looking at, Doctor? You weren't looking at all these other kidney pathologies that were reported to the FDA?

A No. I -- I mean, I looked at the entire report --

MR. PENNOCK: Note my objection to form.

I'm sorry. Go ahead.

A I looked at the --

MR. PENNOCK: Foundation.

A I looked at the entire report and at the entire data, and that was data that stuck out to me. And, therefore, I decided to request the kidney sections of that study.

BY MR. MIZGALA:

Q Okay. Let's go back to the report, Exhibit 13.

MR. MIZGALA: Let's see. Where are you?

Let's go down. Keep going.

Right there.

BY MR. MIZGALA:

Q And you say, "After examining the available mice pathology sides, it is my opinion that dosed mice of both sexes showed more extensive tubular lesions than controls and that these lesions represent lansoprazole-associated renal injury that were not accurately categorized by the reviewing pathologist."

Right?

A Yes.

Q So the reviewing pathologist got it wrong? Is that what you're saying?

A Yes.

Q Was he -- do you know who the reviewing pathologist was?

A I would need to go back to the report and look at the personnel list.

Q Okay. You have no -- do you have any

information about that person's experience reviewing man -- mouse pathology?

A I assume that that person has a certain expertise. Otherwise, he or she would not be in the role of reviewing these kidney sections.

But I don't remember off the top of my head what the name of the person was and what their experience was. I was not provided with a CV.

Q Can you tell me how many mouse two-year oncogenicity studies you reviewed before you reviewed this one?

A I don't know off the top of my head. I would need to go and find out about that.

Q Where would you need to go to find out about that?

A Oh, I would need to go back here to the list -- I don't know whether I looked at a similar study before this. I don't know in which order I reviewed.

So if you ask me, Have you reviewed a similar study before?

I -- I may have reviewed another similar study, you know, in the context of this review before that I just don't remember off the

top of my head and which timely sequence I reviewed which report.

Q Outside of this litigation, Doctor, how many two-year mouse oncogenicity studies have you reviewed?

A None.

Q How about two-year rat oncogenicity studies, outside of this litigation, how many have you reviewed?

A None.

Q And, again, you -- you don't have any -- you have your mental notes, but you don't have any tabulation of your review of the pathology from this study; correct?

A Correct.

MR. MIZGALA: Okay. Let's go to page 14.

BY MR. MIZGALA:

Q Oh, Doctor, before I forget: The -- the images you reviewed, you called them virtual slides?

A Yes.

Q So they were sufficient for your purposes --

A Yes.

Q -- in this -- okay.
And, in fact, you took screen shots, and you included them here to demonstrate the pathology you observed; right?
A Yes.
Q Okay. And these are the kind of things you see in journals, publications all the time; right?
A I also see them in practice. I see tubular injury every day.
Q No, no, no.
I mean, the, you know, photomicrographs, whatever images, they get published all the time in -- in journals; right?
A Yes.
Q Okay. You've probably submitted some to journals; is that correct?
A Yes.
Q Okay.
MR. MIZGALA: Okay. Keep going down.
Okay. Stop right there.
BY MR. MIZGALA:
Q A-29-1979, another "Two-Year Oral Oncogenicity Study in Mice."

Right?

A Yes.

MR. MIZGALA: Okay. Let's go down.

Next page.

Okay. Right there.

Keep going down. I'm sorry.

Okay. Stop.

BY MR. MIZGALA:

Q And the information you have here, Doctor, about how the study was conducted, the macroscopic and the microscopic observations, those were taken from the study report; correct?

A Yes.

MR. MIZGALA: Okay. Let's pull up A-29-1979 (renal), please, and mark that as the next exhibit.

(Whereupon, Exhibit No. 18, Scientific Report No. R&D/93/547 and Table 10, Bates Nos. TAKPPI-INDNDA-01082859 through TAKPPI-INDNDA-01082865, was marked for identification.)

BY MR. MIZGALA:

Q Okay. Doctor, do you see there on the

top A-29-1999, "Two-Year" -- "Two-Year Oral Oncogenicity Study of" -- "in Mice of Lansoprazole."

Right?

A Yes.

MR. MIZGALA: Okay. Let's go down to the table. Keep going.

Okay. We're going to rotate that.

Okay. Go down a little bit.

Okay. Keep going down. Okay.

BY MR. MIZGALA:

Q And there's a -- a -- the line again, "Nephritis, interstitial, chronic."

Right?

A Yes.

Q Okay. And, again, there's 55 control rats with that pathology; right?

A Right.

Q Okay. Fifty-six in the 15-milligram dose; right?

A Yes.

Q Fifty-three -- or forty-three in the 75-milligram dose; right?

A Yup. Yes. Yes.

Q Forty-seven in the 150 --

A Yes.
Q -- correct?
And 47 in the 300; right?
A Yes.
Q No dose-dependent effect; right?
A Right.
Q Okay. And, again, this was submitted to the FDA; right?
MR. PENNOCK: Objection.
A I believe so, yes.
BY MR. MIZGALA:
Q Okay. Let's go back to your report at page 18. Okay. So let's talk about the next study, A-29-438, "A One Year Oral Gavage Toxicity Study of AG-1749 in Rats."
Right?
A Yes.
Q And AG-1749 you understand to be lansoprazole; correct?
A Yes.
Q You say in the second full paragraph, "Compared to the control groups, the animals administered study drug showed significant dose-dependent increase in" -- "in inflammatory infiltrate and acute tubular injury (ATI)."

Right?
A Yes.
Q Okay. So you did observe inflammatory infiltrate and ATI in control animals; right?
A One moment, please.
I did observe focal inflammatory infiltrate as shown in Figure 5 of the control animals. I did not observe significant tubular injury.
Q Okay. The inflammatory infiltrate that you saw in the control animal, that was not caused by lansoprazole; right?
A No.
Q Okay. And you said you didn't see significant tubular injury. Did you see any tubular injury?
A No, I did not.
Q None whatsoever?
A None whatsoever.
Q Okay. And -- and going back -- I'm looking at -- so when you -- you said here, "As seen in Figs 2 and 3 below." That's a typo; right?
A That's a typo, yes.
Q Okay. That should be 5 and 6?

A Five and six, yes.

Q Okay. And you said, "Dose-dependent increase."

Again, did you calculate a dose-response curve?

A Well, dose-response curve, I don't think that that is necessarily the right term because that's more a pharmacological term about the physiological dose accumulation in serum. That's not what we would do.

What we report is the pathological lesion that increases in extent in the increasing dosage that the animals have been exposed to.

Q Right.

And did you do any sort of calculation or is that, again, based upon your mental notes?

MR. PENNOCK: Objection.

A I -- it's -- it's not a calculation. It's a severity of the lesion, which is clearly documented in the images, in the increasing dose group.

So that per se in the pathological realm of medicine is sufficient to say if I can see with higher dosage more severe lesion, that that is a dose dependency.

BY MR. MIZGALA:

Q But you did not tabulate that anywhere, did you?

A I did not tabulate that, no.

Q Right.

You didn't do something like what we just looked at, that table?

A I don't think it's necessary.

Q Why do you -- why do you not think it's necessary?

A Because --

MR. PENNOCK: Why are you -- why are you snickering?

A Because the extent of the lesion is clearly visible in the images. And in pathology, visual evidence is sufficient to prove that a lesion is more severe and extensive compared to -- as control. And that's what I'm showing in my report.

BY MR. MIZGALA:

Q Okay. And you say, in your opinion, "lesions in the kidney tissue were more severe in female animals compared to males."

Right?

On page 18.

A Yes, that's true.

Q Okay. And then you say, "All of these findings."

What are you -- what are you referring to there when you say, "All of these findings"?

A What I want -- what -- what I mean by "all of these findings" is a summary of the lesions, the tubular injury with cast formation, the interstitial inflammatory increase, the degree of inflammatory infiltrate in the interstitium.

So all of these pathologic features were increased in a dose-dependent fashion and especially in female animals. That's what I wanted to express.

Q Okay. And, again, you think whoever -- the pathologist who was reviewing this study got it wrong; right?

A Yes, I do.

Q Okay. Any evidence that the FDA agrees with your conclusion here?

MR. PENNOCK: Objection. No foundation.

A I -- I -- I don't know what the FDA would think, but I think I can assure you if I showed them these tissue sections, they would be

very concerned.

BY MR. MIZGALA:

Q Do you have any intention of doing so?

A No, not --

Q Why not?

MR. PENNOCK: Will you release him from the confidentiality that you required on these materials?

MR. MIZGALA: FDA has got these materials.

MR. PENNOCK: No, they don't have them.

MR. MIZGALA: They don't have his report. They have the materials, though.

MR. PENNOCK: No. I -- I just want to know. If you release him from -- my expert from all confidentiality, we're happy to take it to the next step if you want us to.

MR. MIZGALA: No. I can't do that.

MR. PENNOCK: Okay. Objection.

BY MR. MIZGALA:

Q Doctor --

(Whereupon, the court reporter requests clarification.)

MR. PENNOCK: It's okay.

MR. MIZGALA: Let's go to page 21, please.

Okay. Blow up the bottom. Go to the bottom.

BY MR. MIZGALA:

Q Okay. You say, in your opinion, "The pathological findings in the kidney tissue sections" --

A I think that's a typo again.

Q Okay. What should that be?

A So that would be Figures 7 -- Figure 6 and 7.

Q Okay. Thank you.

And, again, you're referring to "inflammatory infiltrate, tubular casts and signs of acute tubular injury."

Right?

A Yes.

Q And when you say "signs of acute tubular injury," to what are you referring?

A I'm -- I'm referring to the evidence of sloughed-off tubular epithelial cells, the loss of

brush border, the loss of nuclearity of tubular epithelial cells, the dilated tubules, the flattened epithelium. So the criteria of acute tubular injury.

Q Okay. And you say these were misinterpreted as CPN; right?

A Yes.

Q And you note that, "CPN is a chronic, degenerative disease in old rats, that usually manifests with chronic changes of tubular atrophy and glomerulosclerosis."

Right?

A Yes.

Q Okay. And, again, what you're saying is that the pathologist who reviewed this got it wrong; right?

A Yes.

Q Okay.

MR. MIZGALA: Let's go to page 22.

BY MR. MIZGALA:

Q Okay. Now, we have a RD -- R&D/90/339, "Three-Month Toxicity Study of Lansoprazole Administered Orally to Rats (with a One-Month Recovery Period)."

Right?

A Yes.
Q Okay. The information that you included on this page about the study design in study tables 17 and 18, that was all included in the study report submitted to the FDA for drug approval; correct?
MR. PENNOCK: Objection.
A I believe so.
MR. MIZGALA: Okay. And go down. Okay. Oh, let's see.
Keep going. Okay.
Go back up a little.
Okay. Right there.
BY MR. MIZGALA:
Q In the -- so there was a reported increase incidence in nephritis in these study -- in this study; correct?
A Yes.
Q But it was only in the males, 150, 300, and 600 milligrams per kilogram; right?
A Yes.
Q 150 milligrams per kilogram per day in a mouse is 30 times the human therapeutic dose; right?
A But this is rats. That's a rat study;

right?

Q Oh, rat. Yeah.

One -- 150-milligram per kilogram per day in a rat is 30 times the human therapeutic dose; right?

A So, again, I'm not an internist, and I'm not a pharmacologist. So I do not know the drug concentrations in humans very well, but I believe what you're saying may be true.

MR. MIZGALA: Go down. Okay. Hold on. Hold on.

Oh, no. Keep going. Sorry.

Where is it? Keep going.

Okay. Right -- right there.

BY MR. MIZGALA:

Q Again, you disagree with Dr. Levin's interpretations of these findings; is that correct?

A Yes, that's correct.

Q Okay. You say, "These findings were not seen in the [sic] control groups and they indicate a drug-related etiology of the tubular injury and the inflammation."

Right?

A Yes.

Q Okay. So you didn't see any tubular injury or inflammation in the control group; is that correct? Or was that the tubular basophilia and the small crystals you didn't see in the control group?

A One moment, please.

MR. PENNOCK: Note my objection.

Go ahead.

A Yeah. So what I wrote was that in my review of the kidney sections, I -- I saw tubular basophilia, small crystals, and an associated inflammatory infiltrate, and I did not see those in the control group.

That -- that is correct, yes.

BY MR. MIZGALA:

Q Okay. And, again, you say, "These findings should have led to more detailed studies regarding the effect of lansoprazole on kidney tissue in order to obtain a better understanding of renal injuries that were present."

Right?

A Yes. That's true.

Q Okay. And the studies -- the additional studies you would have -- the detailed studies, are those the ones you described to me

earlier?

A Yes.

Q Okay. You mentioned some of those studies would involve rats with an -- you know, an AK -- A -- AKI model or rats that were renally compromised; right?

A Yes.

Q Why would you do that?

A So sometimes when you want to examine a pathological mechanism on the kidney, it is beneficial to induce a slight, not a severe, injury in order to augment the signal.

So in other words, for instance, if you did a study to examine the effect of lansoprazole on the development of progression of chronic kidney disease, you might want to chose a so-called CKD model, which you would choose to do in a mild form, not the most severe form, and then add or leave off the drug in different concentrations to see whether the drug augments the progression towards chronic kidney disease.

That -- that would be an example how you would want to test the effect of a proton-pump inhibitor on kidney lesions, kidney disease progressions such as progression towards CKD and

end-stage renal disease.

Of course, you would also include normal, healthy animals, and you could do physiological manipulations such as dehydration, such as models that are hypertensive spontaneously, and see the effect of the drug.

So we have a number of known pathological models that we can use to test the effect of drug on the kidney.

Q Doctor, you -- you told me earlier that you read the labels for lansoprazole; right?

A Right.

Q Okay. So you're aware that lansoprazole was tested in renally impaired patients; right?

A Right.

Q And it was determined that no dosage adjustment was required in those patients; right?

MR. PENNOCK: Objection. This is well beyond the scope.

Go ahead.

A Yes, I believe so.

BY MR. MIZGALA:

Q Okay.

MR. MIZGALA: Okay. Page 24.

BY MR. MIZGALA:

Q The next study, R& -- R&D/91/1641, "13-Week Oral Toxicity Study in Mice of Lansoprazole."

Right?

A Right.

Q And the information you have on this page is what you took from the study report submitted to the FDA; right?

A Yes.

Q Okay.

MR. MIZGALA: And go down.

Let's see. Keep going.

No. Go back. I went too far.

Sorry.

There you go. Stop right there.

Now, where is that?

Go up a little, please.

No. It's got to be down.

No. Wait. Sorry.

Okay. Sorry.

BY MR. MIZGALA:

Q The second full paragraph, you say, "During my review of the clinical study report, I noted" -- "I noted microscopic pathology findings

indicative of acute and chronic kidney injury in the kidneys of male and female mice from Group 6 that prompted me to request the underlying pathology slides."

Right?

A Yes.

Q Okay. So, again, it was -- it was information in the study report that made you ask for the slides; right?

A Correct. Yes.

Q Okay. And the -- where it says, "These findings include chronic nephritis, bilateral nephrosis, basophilic tubules and vacuolation of epithelium" -- "of epithelium in of proximal convoluted tubules," that was what you got from the study report; right?

A Yes.

Q Okay. And the Group 6, that group was the one getting 2400 milligrams per kilogram per day; right?

A Yes.

Q And are you aware that's about 320 times the human therapeutic dose?

A Yes.

Q Okay. And those findings were in a

total of four mice; right?

A I believe so.

Q Okay. And you don't say this was a dose-dependent effect; right?

A That is correct.

MR. MIZGALA: Let's go down to page 26.

Keep going. Okay.

BY MR. MIZGALA:

Q And you say, "The kidney lesions" -- "kidney" -- "the kidney injury lesions I detected in my review were not chronic but rather consistent with acute tubular injury due to drug toxicity."

Right?

A Yes.

Q Okay. And you say, "Moreover, the lesions were quite extensive and not 'trace' as described in the report."

Right?

A Right. Yes.

Q Okay. So -- and then you say it is also your opinion "that the study investigators misinterpreted the severity and the acute nature of the lesion" -- "acute nature" -- "nature of the

lesions seen."

Right?

A Yes.

Q They got it wrong again; right?

A Yes.

Q Okay. A-29-2142, "Thirteen-week IV [sic] Study" -- "Intravenous Toxicity Study of AG-1749 for Injection in Rats."

Right?

A Yes.

MR. MIZGALA: And if you go -- just keep scrolling down. Go -- go slowly so the doctor can see.

Right there.

BY MR. MIZGALA:

Q You say, "I was not provided the pathology data for this study as requested."

Correct?

A One moment, please.

Yes. That's true.

Q Okay. So all the information you have on -- on pages 27 through 30, including the photos, those were all taken from the study report submitted to the FDA --

MR. PENNOCK: Objection.

BY MR. MIZGALA:

Q -- correct?

A I believe so, yes.

MR. MIZGALA: Okay. And if you -- let's see. Where is that? Page 30.

A Yes.

BY MR. MIZGALA:

Q Okay. Again, there's a picture of gross pathology; right?

A Yes.

Q That was included in the study report; right?

A Yes.

Q Okay. And then you say, "It is my opinion that the above represent pathological changes that are consistent with a classic drug-induced tubular injury. These findings raise significant doubt that the tissues were reviewed by a competent renal pathologists."

A Yes.

Q Okay. So you're saying whoever reviewed this got it wrong; right?

A Yes.

Q Any idea how the FDA missed this?

MR. PENNOCK: Objection. No

foundation. Objection. Form.

A Again, I cannot speak for the FDA. I do not know their process. I cannot speak for the FDA. I'm sorry.

BY MR. MIZGALA:

Q Okay. But you were able to -- to determine that there was an incompetent renal pathologist looking at this study just by looking at the study report; right?

A I can assure you that a competent renal pathologist would not have missed this. And I assume that the person -- the pathologist that reviewed the study result was likely not trained in renal pathology. And that is not unusual, especially if they are a Ph.D. or veterinarian doctors. They may not have done a renal pathology-specific fellowship that would give them the knowledge to assess these lesions.

Q And what training have you received in mouse renal pathology?

A I have received training through experience. I have conducted dozens of experiments in mice, and I have looked at hundreds and hundreds of mouse kidney sections and different pathological injury models and

respective control animals.

And I can assure you that the normal mouse kidney looks completely normal, and I have never seen CPN in mice that I have looked at.

And I can also assure you that the, for instance, tubular injury lesion in mice looks completely identical to the human tubular injury lesion.

Q And do you know anything -- the -- the -- the pathologist who reviewed this study, do you know -- have any idea what training they had in mouse pathology?

A No.

Q Do you know how many --

A I --

Q -- slides they ever reviewed?

A No.

Q But you're willing to call them incompetent?

MR. PENNOCK: Objection.

A I'm willing to call them inadequately trained to recognize these lesions.

BY MR. MIZGALA:

Q Page 30, down at the bottom there, 70 -- 774-010, "A 3-Month Oral Toxicity Study in

Preadolescent Dogs using Lansoprazole'; right?

A Yes.

Q And, again, another study that was submitted to FDA as part of the drug -- drug approval process; right?

A I believe so.

Q Okay. And you say --

MR. MIZGALA: Go down.

Okay. Right there. Stop.

BY MR. MIZGALA:

Q You say, "After reviewing the slides from this study, it is my opinion that these findings were not correctly interpreted."

Right?

A One moment, please.

Yes. That's true.

Q Okay. So they got it wrong again; right?

A Yes.

Q And then you say "the findings are more properly characterized as tubular injury (see below)." And you have a couple slides there; right?

A Yes.

Q Okay. And it's tubular injury and

vacuole -- vacuolization?

A Yes.

Q And then tubular injury and basophilic dysplasia; right?

A Yes.

MR. MIZGALA: Okay. Go to page 32.

BY MR. MIZGALA:

Q You say, "These findings should have raised the suspicion of lansoprazole-dependent tubular injury especially since cytoplasmic vacuolization is a well-known finding in acute drug toxicity of other medications, such as cyclosporine or contrast media."

And you cite a couple things there; right?

A Right.

Q Okay. The -- the -- the things -- the two things you cited, 2 and 3, the first is an article by Naughton, "Drug-Induced Nephrotoxicity," from 2008; right?

A Yes.

Q And then No. 3 is an article by Perazella, "Renal vulnerability to drug toxicity," 2009; right?

A Yes.
Q Okay. Your 2010 case report on omeprazole and AIN --
A Yes.
Q -- makes no mention of cytoplasmic vacuolization; right?
A Right.
Q Are you aware of any case report of a PPI being associated with cytoplasmic vacuolization?
A In humans?
Q Yes.
A I'm not aware of an article that quotes cytoplasmic vacuolization in conjunction with PPI treatment in humans, I believe.
Q And you're -- and are you aware that neither Naughton or Perazella in their articles mentions cytoplasmic vacuolization?
A I'm -- I'm not aware. I believe that in their discussion on cyclosporine in contrast media, they mention cytoplasmic vacuolization.
Q Well, Perazella doesn't even mention cyclosporine in his article, does he?
A I -- I believe that he covered the -- in that article also cyclosporine.

Q Okay. Doctor, would you agree that acute kidney -- kidney injury consists of a group of diseases characterized by a loss of kidney function?

A Yes.

Q And a major challenge in the clinical care of patients with acute kidney injury or AKI is "differating" -- differentiating between its underlying etiologies such as acute tubular injury and acute interstitial nephritis; correct?

A Correct.

Q And acute tubular injury does not have any disease-specific therapies; correct?

A Well, if you call hydration -- if you don't call hydration a disease-specific therapy, then I guess, no, there's no disease-specific therapy.

Q All right. And AIN is treated through withdrawal of the offending agent and immunosuppressive therapy; correct?

A Correct.

Q And, Doctor, not all drugs that affect the kidney do so in the same way; correct?

A Correct.

Q Some drugs act by affecting the

hemodynamics of the kidney; correct?

A Correct.

Q For example, cyclosporine and the other calcineurin inhibitors cause dose-dependent vasoconstriction of the afferent arterioles leading to renal impairment in at-risk patients; correct?

A That is one of the mechanisms how cyclosporine can injure the kidney. Cyclosporine also has a direct tubular toxic effect.

And that is well-known and that is exactly what I referred to, that the cytoplasmic vacuolization is a hallmark lesion of acute cyclosporine toxicity to the kidney tubule.

Q And that should be in either Naughton or Perazella; is that right?

A I'm not sure whether they would be that descriptive in detail like I just mentioned, but I can assure you that if you ask ten nephrologists, What is the hallmark lesion in tubules of acute cyclosporine or contrast media?

All ten of them will tell you cytoplastic vacuolization.

So it is that well-documented, that common that, you know, it doesn't really need

further discussion, in my opinion.

Q And, Doctor, drugs that -- with antiprostaglandin activity, such as NSAIDs, or those with anti-angiotensin II activity, such as ACE inhibitors or ARBs, can interfere with the kidney's abilities to regulate glomerular -- glomerular pressure and decrease GFR; correct?

A Correct.

Q And then, as you said, there are other agents that can cause tubular toxicity such as "amedium" -- aminoglycosides and radio contrast; right?

A Right.

Q And there are still other drugs that are associated with acute interstitial nephritis; correct?

A Correct.

Q So is -- there is no one common path to drug-induced renal toxicity; correct?

A Correct.

Q And, Doctor, do you know Dr. Perazella?

A Yes, I do.

Q How do you know him?

A He is a nephrologist at Yale University, Department of Internal Medicine,

section of nephrology.

Q One of your colleagues at Yale; right?

A Yes.

Q Okay. And you've published with him before; right?

A Yes.

Q Okay. And he's recognized as one of the authorities on drug-induced kidney injuries in humans; right?

A Yes.

Q Okay. Have you talked to him about PPIs and the potential effects on the human kidney?

A No.

Q You're aware he's written on that topic, though; right?

A Yes.

Q Why didn't you include that in your references in this -- in your report?

A I did not see any necessary -- necessity to involve Dr. Perazella in consulting on these animal studies.

Q Okay. With respect to drug-induced kidney injuries in humans, would you defer to Dr. Perazella on that topic?

A Can you repeat the question?
Q Yeah.
With respect to drug-induced kidney injuries in humans, would you defer to Dr. Perazella on that?
A In what context refer or defer?
Q Whether it's happening or not.
A So if I understand your question correctly, whether PPIs cause acute tubular toxicity, I would defer to Dr. Perazella in humans? Is that what you're asking?
Q Yes.
A Yes.
Q Okay.
MR. MIZGALA: Okay. Let's go back to page 32.
BY MR. MIZGALA:
Q Right here, the -- the -- the next study, TAP-TA-03-805, "A-Four-week Oral (Gavage) Toxicity Study of Lansoprazole in Neonatal Rats."
Correct?
A Sorry. On which -- which page are you? Sorry.
Q Page 32. Bottom of the page.
A Yes, that's right.

Q Another study submitted to FDA as part of the drug approval process; correct?
A I believe so.
Q And once again, you -- you think the pathologist who was reading the study got it wrong; right?
MR. PENNOCK: Wrong or right?
MR. MIZGALA: He thought -- he thought he got it wrong.
BY MR. MIZGALA:
Q Correct?
MR. PENNOCK: Objection to form.
A One moment.
Yeah. I mention in my report that the study pathologist is not reporting the dose animals' kidney pathology.
BY MR. MIZGALA:
Q So you think he got it wrong -- she/he?
A Yes.
Q Okay.
MR. MIZGALA: Let's go to page 35.
A Yes.
MR. MIZGALA: Go down, please.
Okay.

BY MR. MIZGALA:

Q Okay. The findings, again you talk about that you -- you discovered consisted of acute tubular injury, inflammatory interstitial infiltrate, tubular cast formation and glomerular amyloid deposits; right?

A Yes.

Q Okay. And then you say, "Moreover, several of the animals in different Takeda studies showed extensive green intratubular crystal deposits" --

A Yes.

Q -- right?

Have you ever seen green crystals in a human renal biopsy?

A I may have seen in the past 20 years one or two cases where abnormal green crystals were seen, yes.

Q And did you attribute them to anything?

A I could not attribute them to anything.

Q Okay. Have you seen a case report in a human describing green intratubule crystals upon taking a PPI?

A No, I have not.

Q Okay.

MR. MIZGALA: And next page.

BY MR. MIZGALA:

Q Top you say, "These findings, many of which were dosage-dependent" -- "dosage-dependent."

Which of the findings were dosage -- dosage-dependent?

A The tubular injury.

Q Any others?

A And the interstitial infiltrate also was dose-dependent.

Q Okay. But, again, you don't -- you didn't tabulate the results of your review anywhere or any study; correct?

A Correct.

Q Then you say "are indicative of direct drug toxicity to the kidneys in the form of acute tubular injury or tubulointerstitial nephritis."

Right?

A Uh-huh. Yes.

Q Okay. Which of the findings that you have listed are indicative of acute tubule -- tubular injury?

A So all of the images that show -- that I described as acute tubular injury by dilated

lumen, flattened epithelium, loss of nuclearity, loss of brush border, sloughing of individual epithelial cells, all these features that we have gone over in all these studies, those are the features that I attribute to acute tubular injury.

Q Okay. So all the findings you listed above on the -- on the prior page are what you say are indicative of acute tubular injury; right?

A As I described in the reports pertaining to the respective images, yes.

Q Okay. Okay. You also mentioned tubulointerstitial nephritis here.

A Yes.

Q First time in your report.

A Well --

Q Why?

A I -- so in the above-discussed reports, there was interstitial infiltrate that in some studies was increased by dosage. And in the images, I described them as inflammatory infiltrate.

However, here in the analysis interpretation part, I argue that they are indicative of acute interstitial nephritis. And it is not unusual to have acute interstitial

nephritis seen in conjunction with acute tubular injury or crystal deposits for that matter.

So in other words, I argue that the interstitial infiltrate may possibly constitute a drug-induced interstitial nephritis.

Q It may, and it may not; right?

MR. PENNOCK: Objection.

A More likely may.

BY MR. MIZGALA:

Q And what makes that more likely?

A The fact that it's dose-dependent.

Q Based upon your mental notes; right?

MR. PENNOCK: Objection.

A Based upon these very disturbing images that I found so many of and put in this report that is really depressing to see from a major pharmaceutical company, in my opinion.

BY MR. MIZGALA:

Q You know you mentioned ethics yesterday, Doctor, that you didn't think something was ethical.

What's that -- what standard is that based on? Is that based on your standard?

MR. PENNOCK: Objection.

What -- what are you talking

about? He didn't mention ethics just now.

If you have testimony that you want to talk to him about, pull it up. Otherwise, he's not answering the question.

BY MR. MIZGALA:

Q Doctor, do you have a standard of ethics that's codified somewhere?

MR. PENNOCK: Objection. Form. Foundation.

A Yes, I do.

BY MR. MIZGALA:

Q And where is that codified?

MR. PENNOCK: Objection. Form. Foundation.

This is really just harassing the witness. So we can stop the deposition and have the special master continue to sit in on it or you can stop harassing --

BY MR. MIZGALA:

Q Well, Dr. Moeckel, what --

MR. PENNOCK: Stop harassing him or we'll suspend the deposition under

the rule, and I'll ask for a master to sit in on the rest of the deposition. So don't -- listen, don't start harassing him.

BY MR. MIZGALA:

Q Doctor, are you going to provide --

MR. PENNOCK: Don't start harassing him. You just asked him where's his code of ethics codified. Okay. Do not harass my witness or we will suspend it.

MR. MIZGALA: Paul -- Paul, stop.

MR. PENNOCK: That's it. Withdraw your question and move onto some actual substantive questioning as you have been doing for the last three hours.

MR. MIZGALA: He made a comment about the behavior of a pharmaceutical company.

BY MR. MIZGALA:

Q Are you going to be offering that opinion at trial?

MR. PENNOCK: That is a different question. Go ahead. Yes.

Go ahead, answer -- ask the next

question.

MR. MIZGALA: Is he going to offer that opinion at trial?

MR. PENNOCK: Absolutely.

MR. MIZGALA: Absolutely?

MR. PENNOCK: Sure. Why not?

BY MR. MIZGALA:

Q And, Doctor, what's the basis for that opinion? How can you say -- how -- what's your basis for assessing the propriety of the actions of a pharmaceutical company?

A Well --

MR. PENNOCK: Objection to form. Foundation.

Go ahead.

A Well, I observed in these kidney sections significant dose-dependent injury that were not further examined and evaluated and that I find unusual.

BY MR. MIZGALA:

Q Okay. Doctor, the -- the -- other than the inflammatory infiltrate, is there any other finding that you consider to be indicative of tubulointerstitial nephritis?

A No.

Q Okay. The next sentence, you say the -- "These findings are consistent with drug-induced kidney injury pathology in human kidney biopsies."

Right?

A Right.

Q Okay. Which -- are you referring to all those findings you had identified above or specific findings?

A I am referring especially to the acute tubular injury and the interstitial infiltrate.

Q Okay. And -- and we talked earlier about how drugs affect the kids -- the kidneys differently.

Which drugs -- when you say "drug-induced," which drugs are you referring to?

A I'm referring to proton-pump inhibitors.

Q Well, you say, "These findings are consistent with drug-induced kidney injury."

Are you saying -- are -- are you referring to PPIs there or are you referring to other drugs?

A So I want to -- I have to clarify my -- my answer.

I am referring, A, to other drug-induced and well-known lesions, such as acute tubular injury and interstitial infiltrate, interstitial nephritis, both of which are well-known lesions caused by drugs.

But I also have read articles that show interstitial nephritis associated with PPIs. So to a certain degree I associate it also with PPIs.

Q And -- and, Doctor, acute interstitial nephritis is a subset of acute kidney injury; correct?

A Yes.

Q Okay. So, Doctor, just because you see inflammatory interstitial infiltrate, that doesn't necessarily mean that it's secondary to AIN; correct?

A Can you repeat that question, please?

Q Just because you see inflammatory infiltrate -- interstitial inflammatory infiltrate, that doesn't mean it was secondary to AIN; correct?

A Correct.

Q Okay. Let's -- okay. The next, "Early drug-induced kidney damage shows infiltration of inflammatory cells and, if the process of damage

continues without removal of the offending" -- "offending agent, then the renal interstitial infiltrate becomes more diffuse."

Right?

A Yes.

Q And you cite the Chen article for that; right?

A Yes.

Q Now, the Chen article, that wasn't listed -- limited to PPIs; correct?

A One moment. Let me just in particular look and refresh my memory.

Yes.

Q Yes, it was not limited to PPIs; right?

A Right.

Q Okay. In fact, they conclude that antibiotics are the main causes of drug-induced AIN; right?

A I don't remember off the top of my head. This has been a while since I read this article, but it may be correct that they mention or describe it or articulate it in that form.

Q Okay.

MR. MIZGALA: Let's pull up, Jeff, 4, the 2012 Chen.

BY MR. MIZGALA:

Q Okay. This is the Chen article you reference; correct, Doctor?

A Correct.

Q Okay.

MR. MIZGALA: Let's go to the end. Right -- oh, yeah. Right there. Right there, that paragraph, "In summary." Go up.

BY MR. MIZGALA:

Q They conclude: In summary, antibiotics are the main causes of drug-induced AIN; correct?

A That's what they write, but it's not a correct sentence, actually.

Q Okay. Let's go back to their data.

COURT REPORTER: Is this being marked as an exhibit?

MR. MIZGALA: Yes.

(Whereupon, Exhibit No. 19, "Delayed Renal Function Recovery From Drug-Induced Interstitial Nephritis," was marked for identification.)

MR. MIZGALA: Okay. Right there. No. Keep going back. Keep going.

No. Down. Down. Down. Down.

Keep going.

Right there. Okay.

BY MR. MIZGALA:

Q "The offending-drug distributions in all patients."

Right?

A Right.

Q Okay. Thirty-six to antibiotics; correct?

A Correct.

Q Eight to NSAIDs; right?

A Right.

Q And NSAIDs are nonsteroidal anti-inflammatory drugs like Motrin; is that correct?

A Can you repeat the question? You broke up.

Q NSAIDs is nonsteroidal anti-inflammatory drugs; right?

A Yes, sir.

Q Like ibuprofen; right?

A Right. Yes.

Q Okay. And then they have herbs?

A Yeah.

Q Okay. And then PPIs; right?
A Right.
Q Okay.
MR. MIZGALA: Let's go back to his report. Blow that up a little.
Stop.
BY MR. MIZGALA:
Q Okay. The sentence, "As renal damage progresses, tubular cell" -- "cell necrosis, tubular atrophy, and loss of tubules can be seen in human biopsies."
Right?
A Yes.
Q Okay. When you say "renal damage" there, what are you referring to?
A I'm referring to pathological lesions injuring the kidney.
Q Okay. Is this -- is this acute tubular injury or something else?
A One moment.
So this is referring in the context of acute tubular injury and interstitial nephritis, which both can be caused by drugs, that if the drug injury continues, then you have progression and extension of the tubular cell necrosis, the

atrophy, and loss of tubules. That is a very well-known and well-defined mechanism in humans.

Q Okay. And under what circumstances would renal damage progress?

A There are many circumstances under which renal damage can progress.

You would say, in general, that persistent drug injury would enhance progression. There may also be still unknown genetic factors that are being elucidated currently that might facilitate progression of injury.

Q Okay. Are you -- and I'm -- I'm referring to this specific context, Doctor, where you think PPIs in these animals were causing, you know, acute tubular injury.

What would cause that to progress?

A The persistent offending drug.

Q Okay. And that would be true for AIN; right?

A Yes.

Q And Doctor, you cite -- what you cited for that were references 5, 6, and 7; correct?

A Yes.

Q Okay. And none of those are specific to PPIs; correct?

A They're not specific to PPIs, but they are specific or describe the progression of acute lesions.

Q Right.

That Mann article, 2012, doesn't even mention PPIs, does it?

A I don't recall off the top of my head, but I can check that for you.

Q Okay. Let's go -- you say, the next sentence, "Likewise, tubular crystalline deposit is an established marker of kidney injury produced by nephrotoxic agents such as anesthetic drugs, methoxyflurane, and halothane and antiretroviral medications."

Right?

A Right.

Q And you cite three articles: 8, which is Perazella, 2003; 9, which is Wyeth, 2009, and 10, which is Rho, 2007; correct?

A Correct.

Q Okay. And none of those articles relate to PPIs; correct?

A I believe that is right.

Q Okay. PPIs are not mentioned in any of them; right?

MR. PENNOCK: Objection. Form.

A Again, I don't know off the top of my head. I don't have all of these articles at my ready disposal. So at the moment, I cannot confirm your question.

BY MR. MIZGALA:

Q Are you aware of any -- oh, we already talked about that.

MR. PENNOCK: Are we going to get to a point where we can take a break?

MR. MIZGALA: We can take one now.

MR. PENNOCK: Is this a good time --

THE WITNESS: Yeah.

MR. PENNOCK: -- to have one?

THE WITNESS: Yeah.

MR. PENNOCK: Thank you.

THE VIDEOGRAPHER: Off the record 2:34 p.m.

(Whereupon, there was a recess taken from 2:34 p.m. to 3:09 p.m.)

THE VIDEOGRAPHER: On the record 3:09 p.m.

BY MR. MIZGALA:

Q Doctor, earlier you -- you mentioned

case reports in humans of PPIs and -- and AIN, acute interstitial nephritis; correct?

A Yes.

Q Okay. Are there -- are you aware of any case reports of PPIs and ATN, acute tubular necrosis?

A I believe not.

Q Okay. Doctor, yesterday you said you had reviewed some expert reports in this case.

Have you reviewed the expert report from Dr. Jerry Hardisty?

A And remind me quickly who he is.

Q He's a veterinary pathologist.

A One moment.

I don't remember off the top of my head whether I reviewed his report.

Q Okay. Do you know who Dr. Hardisty is?

A I do not know him personally.

Q Okay. Do you know of him? Do you know of his reputation?

A I do not know much about his reputation.

Q Okay. You know who Dr. John Seely; right?

A I do know -- if you refer to Dr. Seely

who has published on toxicity animal studies, yes, I know who that is.

Q Yeah.

You actually cite -- your 12th reference is Dr. Seely, who is one of the authors of Chapter 11 - Kidney --

A Yes.

Q -- and Boorman's Pathology of the Rat; right?

A Right.

Q Okay. And you're relying in part on that -- in -- you're relying on part on that for your opinions here today; right?

A Right.

MR. MIZGALA: Okay. Let's go to page 37, "Conclusion."

BY MR. MIZGALA:

Q Okay. You say, "It is my opinion as a pathologist and clinician."

What -- when you use "clinician" there, what do you mean?

A I mean a physician who is taking care of patients.

Q Okay. But you don't see patients directly, or do you?

A No, I don't. But as a pathologist, I handle their tissue, and I review and analyze and diagnose diseases of the tissue, which actually in hospital terminology is consistent with patient care.

Q You're -- you're a clinical pathologist; right?

A I'm an anatomic pathologist.

Q Okay. And -- and you're -- and -- and you review human tissues in your day-to-day job; right?

A Right. I review tissue that has -- has just come out of patients.

Q Okay. Doctor, all the preclinical study data that we've discussed and that's discussed in your report was submitted to the FDA; correct?

A Can you repeat that question?

Q Yeah.

The -- the preclinical study -- Takeda's preclinical study today -- let me start again.

Takeda's preclinical study data discussed in your report, all of that was submitted to the FDA; correct?

MR. PENNOCK: Note my objection. Form. Foundation. And it's vague and ambiguous.

A So I do not know for a fact. I assume that it was submitted to the FDA.

BY MR. MIZGALA:

Q Okay. Do you have any basis to -- to consider that it wasn't?

MR. PENNOCK: Objection. Form. Foundation. Vague and ambiguous.

A So, again, you know, I don't work for the FDA. I'm not in contact with the FDA in any way.

So, you know, I -- I -- I have to rely, if someone tells me these were submitted to the FDA, that they were. I personally have not checked and tested whether that actually is true.

BY MR. MIZGALA:

Q And -- and, Doctor, you've seen the lists of the preclinical studies Takeda performed; right?

A Yes.

Q You -- you didn't review every study on that list; right?

A I would say I reviewed many studies off

that list.

Q Doctor, the FDA, in addition to having the preclinical studies for lansoprazole and dexlansoprazole, they also had the preclinical studies for omeprazole, esomeprazole, pantoprazole and rabeprazole; correct?

MR. PENNOCK: Objection to form. Foundation. And it's vague and ambiguous.

A Again, I can only say that I believe. I have no proof. I did not check on that or call anybody at the FDA that that is true.

BY MR. MIZGALA:

Q Doctor, you know there are six PPIs that are currently on the market right now; right?

A Yes.

Q Okay. And they all had been approved by the FDA at one point; right?

A I believe so, yes.

Q Okay. And as part of the FDA approval process, you have to -- you have to submit preclinical testing data, toxicity data; right?

MR. PENNOCK: Objection to form. Foundation. Vague and ambiguous.

A I -- again, I believe that is correct.

BY MR. MIZGALA:

Q Okay. So the FDA has all that data; right?

MR. PENNOCK: Objection to form. Foundation. Vague and ambiguous.

You keep saying "data." You use that in every question. The FDA only gets the preclinical -- preclinical study reports. So -- and -- and your appendices.

BY MR. MIZGALA:

Q Okay. The FDA has all those preclinical study reports and appendices; correct, Doctor?

A I believe so.

Q Okay. Is there any evidence that you've seen that the manufacturers withheld any preclinical data from FDA?

MR. PENNOCK: Objection. Form. Foundation. Vague. Ambiguous.

A Again, you know, I -- I don't know everything. So I cannot speak as to whether the manufacturer may have withheld information.

BY MR. MIZGALA:

Q Any evidence that you've seen that the

FDA disagreed with any of the statements made by any of the manufacturers regarding their preclinical studies?

MR. PENNOCK: Objection to form.

Go ahead.

A Again, I did not see any internal memos by the FDA that describes the discussion during the review of these preclinical studies. So I'm not competent to comment on that.

BY MR. MIZGALA:

Q Any evidence that the FDA has asked any manufacturer to do additional animal studies on the renal effects of PPIs?

A Again, I'm not -- I don't think that I'm qualified to, you know, comment on that because I don't know all the communications between FDA and the pharmaceutical companies.

Q Any evidence that the FDA has requested any manufacturer to amend its labeling regarding the renal findings on its studies?

MR. PENNOCK: Objection.

Foundation. Form.

A Again, I do not have all the internal memos or the communications between FDA and the pharmaceutical company to comment on that.

BY MR. MIZGALA:

Q Doctor, you're aware that the FDA required an update to the AIN labeling of PPIs last year; correct?

A Can you repeat the question?

Q You're aware -- you reviewed the labels.

You're aware that the FDA requested an update to the AIN section of the PPI labeling last year; right?

MR. PENNOCK: Objection. Form. Foundation.

A I believe so, yes.

BY MR. MIZGALA:

Q Okay. And that -- that update had nothing to do with data from animal studies; right?

A I don't have that information. I don't know what triggered the update.

Q Okay. Doctor, is there a generally accepted animal model of CKD?

A Yes. I would say the 5/6 nephrectomy model in rats is a accepted model of CKD.

Q And how about a generally accepted model of AIN in -- in -- in animals?

A I believe there's a snake venom model that causes AIN in study animals.

Q Okay. Doctor, I'm going to show you some photos taken from some of the animals in the Takeda studies, and I'd like you to let me know what pathology, if any, you see.

MR. MIZGALA: So, Jeff, let's start with Figure 1.

MR. PENNOCK: Are these marked as -- as exhibits?

MR. MIZGALA: They're going to be marked as exhibits, yeah.

MR. PENNOCK: So can we -- can we mark them first so we can identify them and refer to them as such?

MR. MIZGALA: Okay. What's -- what are we on, what exhibit?

THE VIDEOGRAPHER: This one is going to be 20.

MR. MIZGALA: Okay. Exhibit 20.

(Whereupon, Exhibit No. 20, Fig 1 - Rat, was marked for identification.)

MR. PENNOCK: Okay.

BY MR. MIZGALA:

Q And -- and -- and, Doctor, if -- if you want, I have a -- I have a higher magnification.

MR. PENNOCK: Excuse me, James.

So somebody has got to put this over the chat.

Oh, there we go. Thank you, Jeff.

MR. MIZGALA: Or you can download it and then you can see it.

THE WITNESS: Which exhibit is it? Which exhibit?

MR. PENNOCK: Twenty.

THE WITNESS: Twenty.

BY MR. MIZGALA:

Q Does that magnification work for you, Doctor, or do you need a higher magnification?

A I think I will need a higher magnification.

Q Okay. Let's go to Figure 2 then.

MR. PENNOCK: And this is Exhibit 21?

MR. MIZGALA: Correct.

(Whereupon, Exhibit No. 21, Fig 2 - Rat, was marked for identification.)

BY MR. MIZGALA:

Q Is there any pathology in that slide, Doctor?

A Unfortunately, I -- you know, it's not -- the resolution is not good enough for me to judge this.

Q Can you identify anything that's going on in that slide?

MR. PENNOCK: Objection. Form. Go ahead.

A Yeah. The resolution is not great. I can tell you that this is kidney cortex with glomeruli.

BY MR. MIZGALA:

Q And the glomeruli are those little round structures; right?

MR. PENNOCK: Objection.

A The glomeruli -- well, there are many round structures on this image. The glomeruli have the typical histological morphology. So I can recognize them.

BY MR. MIZGALA:

Q Okay. Nothing else?

MR. PENNOCK: Objection to form.

A I think the resolution is inadequate

for me to make any kind of judgment here in regard to pathology.

BY MR. MIZGALA:

Q Okay.

MR. MIZGALA: Let's go -- Jeff, let's go to Figure 4. So this will be Exhibit 22.

(Whereupon, Exhibit No. 22, Fig 4 - Rat, was marked for identification.)

BY MR. MIZGALA:

Q Any pathology you see there, Doctor?

A I don't see it at the moment. I'm waiting for the image to be put in the chat. Which exhibit is it? Twenty-two?

MR. PENNOCK: Twenty-two.

THE WITNESS: Yeah.

BY MR. MIZGALA:

Q Twenty-two.

A So I can tell you it's kidney tissue.

Q Okay. There's glomeruli; right?

A Glomeruli are visible.

Q Okay. Any pathology?

A The resolution of these images does not allow any pathological conclusion.

MR. MIZGALA: Jeff, if I shared my screen, would that help or not?

THE VIDEOGRAPHER: You know, I have the original TIFs that you sent over to me. They're the same file size, but I had to convert them to PDF to show them on my screen. I can send the TIFs into the chat for the doctor --

MR. MIZGALA: Yeah.

THE VIDEOGRAPHER: -- to look at if you'd like.

MR. MIZGALA: Yeah. Send the TIF and see if that helps.

THE VIDEOGRAPHER: So that's the same one we're looking at now, Doctor.

COURT REPORTER: Is this being marked as an exhibit?

MR. MIZGALA: It's already marked.

MR. PENNOCK: We -- we need to remark this No. -- or we need to mark it No. 23.

MR. MIZGALA: That's fine.

(Whereupon, Exhibit No. 23, Fig 4 - Rat, was marked for identification.)

MR. PENNOCK: It's noted as Figure 4 - Rat, 8X.tif, 4.44 megabytes.

COURT REPORTER: I show two documents in the chat that are TIF documents. Which one is the exhibit?

MR. MIZGALA: Figure 4 - Rat, 8X.

THE VIDEOGRAPHER: They're both the same, Cliff. I just relabeled it with an exhibit number.

BY MR. MIZGALA:

Q Any better, Doctor?

A It's a little bit better. So I can see glomeruli.

Unfortunately even at the highest magnification, the resolution is not good enough to evaluate tubular injury.

Q Okay.

MR. MIZGALA: Let's try Figure 6 as a TIF, please, Jeff.

BY MR. MIZGALA:

Q Can you see any pathology there, Doctor?

A So is it in the chat?

Here we go. Let me download it and take a look at this.

COURT REPORTER: Marking this as well?

MR. MIZGALA: Yes.

COURT REPORTER: Thank you.

(Whereupon, Exhibit No. 24, Figure 6 - Rat, was marked for identification.)

A So I can make out that it is kidney tissue. I can see glomeruli. There appears to be focal lymphocytic infiltrate.

But, again, when I go in higher power -- and that is probably due to the file -- it becomes very blurry. So, again, tubular cell injury cannot be assessed or any cell high morphologic evaluation cannot be assessed.

BY MR. MIZGALA:

Q Okay. We're going to try one more on the rat.

MR. MIZGALA: Figure 10, please.

This will be Exhibit 25.

(Whereupon, Exhibit No. 25, Fig 10 - Rat, was marked for identification.)

A So, again, here we have kidney tissue. I can see glomeruli. I can see proteinaceous casts. I can --

BY MR. MIZGALA:

Q You can -- what, Doctor?

A I can see proteinaceous casts.

Q Oh, casts, okay.

A And I can see focal lymphocytic infiltrate.

Q Is that it?

A Well, again, the resolution in this, you know, image display at higher power does not allow detailed cell evaluation.

And I want to point out that these images for me to review do, by far, not have the resolution and quality that I'm used to with my Qpath program.

So I can tell you is that there are casts. It's kidney. There's interstitial fibrosis. There seems to be a lymphocytic infiltrate. But beyond that, I cannot do any further detailed evaluation.

Q Okay.

MR. MIZGALA: Let's try Figure 15, Jeff.

(Whereupon, Exhibit No. 26, Fig 15 - Mouse, was marked for identification.)

BY MR. MIZGALA:

Q This is from the mouse, and this is at even a higher power, 20X.

Anything you can see there, Doc?

A And let me download it from the chat again, I think.

Q Of course.

COURT REPORTER: Twenty-six.

A Yeah.

So, again, I can see it's kidney tissue. We have glomeruli. There appears to be a lymphocytic infiltrate in the interstitium. The glomeruli appear to have a pink amorphous material in the mesangium reminiscent of the glomeruli amyloid that we saw in the mice.

Again, the resolution at high power is not great.

BY MR. MIZGALA:

Q Okay.

A It looks like -- it -- it's reminiscent of the sections of mouse kidney that had glomeruli amyloid.

Q Okay.

MR. MIZGALA: Let's do one last one. Figure 18, please.

(Whereupon, Exhibit No. 27, Fig 18 - Dog, was marked for identification.)

BY MR. MIZGALA:

Q This is from a dog at 20X.

Anything there, Doc?

A One moment, I'm just going to --

Q Oh.

A -- download it again.

Q Uh-huh.

A That figure 18 -- oh, here it is. Gotcha. Okay. Just one second, please.

So, again, I can tell you this is kidney. We have two glomeruli in the center. We can see tubules.

Again, the resolution for the cell at detail is not great.

It appears that there is some vacuolization in the cytoplasm of tubules.

Q The tubule -- tubules are the things that look a little like worms; right?

A Exactly. Those are these worm line or curvilinear structures that have the pink cuboidal-shaped cells. The blue areas are the nuclei. Yeah. So those are the tubules.

And then the round structures are the glomeruli. The larger round structures with a little bit of space around the glomerular tuft, which is the Bowman's space. So those are the glomeruli.

Q And when you mentioned "vacuoles," where -- where would those be?

A Again, the resolution is not great.

But it appears that these vacuoles are in the cytoplasm of tubular epithelial cells.

Q Okay. Okay. You can drop that.

MR. MIZGALA: Let's go to the Statement of Compensation, please.

(Whereupon, Exhibit No. 28, Statement of Compensation, was marked for identification.)

BY MR. MIZGALA:

Q Okay. Doctor, have you seen this before?

A Yes.
Q Okay. When did you see it first?
A Oh, a few days ago. I don't remember exactly when.
Q Okay. And based upon your knowledge, is this accurate?
A I believe this is accurate.
Q Okay. So your first bill of 15 hours, was that for time worked or was that a retainer?
A No, that was for -- all of -- all of these charges are for hours worked.
Q Okay. And, Doctor, your first report in this litigation was dated April 22nd of 2021; correct?
A Correct.
Q Okay. So the time from before then would have been spent -- that -- the -- you would have had -- up until that report was done -- I don't know -- a hundred and twenty, a hundred and fifty, a hundred and two -- two hundred and thirty-one hours; right?
A I think a little less than -- how many did you say? Sorry.
Q Well, I got -- so we've got to 4 -- 4/15, we've got 15, 17, 32, 49, 81, 111, and then

another 120.

So 231.

A Yeah. That -- that is about correct.

Q Okay. And then you did your first report.

And that -- that includes your review of the AstraZeneca slides; right?

A Yes.

Q Okay. And when did you get the AstraZeneca slides?

A So I don't remember the correct exact date. I think we can find that for you and send that to you.

But I believe that I received the -- you mean the -- the -- the -- the image files on the drives; is that correct?

Q Yes.

A Yeah. So I believe I received them at the end of February '21.

Q Okay. So the time you would have spent reviewing the AstraZeneca slides and drafting that report would have been captured in the -- the March entry and the April entry; is that correct?

A Yes.

Q Okay. And after you completed the

AstraZeneca report, you got the Takeda slides; right?

A Right.

Q Okay. And you completed your report for -- for -- on the Takeda slides on May 20th; right?

A Right.

MR. PENNOCK: I'm sorry.

Just note my -- you said -- you said that he got the slides after he finished the AstraZeneca report?

MR. MIZGALA: Yeah.

MR. PENNOCK: Do you have -- do you have some basis for that?

MR. MIZGALA: Yeah. The -- the -- the FedEx and your e-mail to me that says send them on Monday, the 25th.

MR. PENNOCK: Okay. And that's when it went? All right.

BY MR. MIZGALA:

Q Okay. Doc, is it -- is it your recollection that you got the -- the Takeda images after you completed your report on AstraZeneca?

A I don't remember for sure.

Q Okay. So you would have spent the May

times -- right? -- the 40 and 30 hours, reviewing the Takeda slides, images; right?

A I think I spent many more hours than that. This is just what I billed. I spent many more hours than I billed.

Q Are -- you're not going to bill for other hours?

A Well, you know, just like, you know, many of good lawyers, I only bill for hours that are billable. And so a lot of the evaluation of the slides and the technical setup, some of these activities I would not bill for.

Q And how many other hours do you think you -- you spent doing that, doing the technical activities and setting things up?

MR. PENNOCK: Objection. That wasn't what he limited it to.

Go ahead.

So object to mischaracterizes.

A I do not remember.

BY MR. MIZGALA:

Q Doctor, when you were reviewing the images, you said you did it -- you did a -- kind of a two-step process, an -- an initial review and then, if it merited, a -- a more extensive review;

correct?

A Correct.

Q Okay. How much time did the initial review take?

A So the initial review was -- depending on the appearance of the slide, could vary from a few seconds to maybe 20 seconds.

So I am very fast in reviewing slides. So that's roughly what it takes, the initial review.

Q Okay. And then the more extensive review and taking pictures, how long would that take?

A I would say, you know -- and this is kind of an estimation -- anywhere between one and three minutes.

Q One and three minutes?

A Yeah.

Q Okay.

A A few minutes really would -- would be long, yeah.

Q Okay. And -- and besides the time you've spent at this deposition, is there -- are there any other hours that you have not yet billed but intend on billing?

MR. PENNOCK: Objection.

He's already answered there are other hours.

MR. MIZGALA: This is -- this is -- I -- I -- this is for anything else that he's not yet billed but he intends to bill.

MR. PENNOCK: Objection. Form. Foundation.

Go ahead. You can answer.

A Besides what you see here on this graph, at the moment, I'm not aware of other hours that I would bill for at this time point. Although, I reserve the privilege that it may change.

BY MR. MIZGALA:

Q Well, you're going to bill for your time in the deposition yesterday and today; right?

A Yes.

Q Okay. Okay.

MR. MIZGALA: Give me a few minutes. I want to take a break. And -- and I may be done.

THE VIDEOGRAPHER: Off the record 3:44 p.m.

(Whereupon, there was a recess taken from 3:44 p.m. to 3:56 p.m.)

THE VIDEOGRAPHER: On the record 3:56 p.m.

MR. MIZGALA: Doctor, first of all, I want to thank you for taking the time to visit with us for the last -- over the last couple days.

THE WITNESS: Thank you.

BY MR. MIZGALA:

Q Your responsibilities at Yale, how many hours a week do you spend on those things?

A So let me elaborate a little bit on this. I'm a -- an attending in renal pathology. I am on service and call 75 percent of the calendar year --

Q Uh-huh.

A -- which equivocates to a hundred percent clinical position. I also have a federally funded research lab that does research on acute tubular injury.

And my time is pretty much spent between the clinical services, the administration of the renal pathology laboratory and electromicroscopy laboratory, and research. Of

course, I also teach residents and medical students.

So that's how I would describe the -- my -- my responsibilities here break up.

Q Okay. And on average, how many hours a week does that require of you?

A I would say that that requires 60 to 70 hours on average.

Q Was that true for May of this year?

A In May I had, I think, two weeks of service. So that means that a significant time that I normally would spend in the year on the kidney biopsy service I did not have to -- have to spend in May.

Q Okay. And how much time would that be?

A So I would -- I would say that -- so you mean how much time I would usually just spend on the clinical service or did I not spend on the clinical service?

Q How much time in May did you not spend on the clinical service?

A Okay. So I would say that that would be a total of at least 60 hours.

Q Okay.

MR. MIZGALA: Okay. Subject to

Mr. Pennock's questioning, I have no further questions at this time.

MR. PENNOCK: Thank you.

I do have a couple things I'd like to talk to you about, Doctor.

CROSS-EXAMINATION

BY MR. PENNOCK:

Q So is -- I understood from your testimony earlier that there are hours that you -- you spent or some period of time that you spent looking and dealing with the Takeda slides that you've not yet billed us for; is that correct?

A That is correct.

Q Okay. All right. And you did not have intention to bill us for those?

A Well, I always try to bill those hours that I think are billable, meaning are involved with the direct analysis of material and, like in this case, slides, and so forth.

Q Okay. You were asked a number of questions throughout the last two days regarding the FDA and what the FDA had in its possession regarding preclinical studies.

Do you remember the questioning about that?

A I remember being questioned about study data that the FDA might have or expertise that the FDA might have.

Q Well, let -- let me ask you a couple questions.

First of all -- and I think you've already said this -- what information, if any, do you have as to whether or not the FDA reviewed the nonclinical -- the preclinical study reports provided to it by these companies?

MR. MIZGALA: Object to form.

A I have no detailed information of whether the FDA --

(Whereupon, there was an interruption.)

(Whereupon, the court reporter requests clarification.)

A I have no detailed information regarding the time spent reviewing these studies or the personnel that might be involved in reviewing these studies. I --

BY MR. PENNOCK:

Q Do you have any -- do you have any

knowledge as to whether or not the FDA reviewed these studies at all?

MR. MIZGALA: Objection.

A I have no knowledge in -- I -- I do not have knowledge whether the FDA reviewed these studies at all.

BY MR. PENNOCK:

Q You have -- withdrawn.

What, if any, knowledge do you have as to whether the slides for these studies that you received were also provided to the FDA?

MR. MIZGALA: Object to form.

A I have no information whether the slides that I reviewed were also shown to the FDA.

BY MR. PENNOCK:

Q I'd ask you to assume that -- for the sake of argument, that the FDA -- someone at the FDA did look at these slides that you reviewed.

Do you have any knowledge as to what their credentials are?

MR. MIZGALA: Objection.

A I have no information regarding the credentials of any experts at the FDA.

BY MR. PENNOCK:

Q Do you know if the FDA, during the time

period that these clinical study reports were being provided to the FDA, had histopathologists on staff?

MR. MIZGALA: Objection.

A I have no information whether the FDA had histopathologists on staff.

BY MR. PENNOCK:

Q You testified several times in response to questions that, in your opinion, the -- whoever reviewed the slides at Takeda came to the wrong conclusions regarding what they were seeing in some of the slides; is that right?

A That's correct, yes.

Q Okay. I'd ask you: What -- what if someone at the FDA reviewed these slides and came to the same conclusion as the Takeda people, what would be your view of the FDA reviewer of the slides, if any view?

A If I don't know the reviewer and I cannot evaluate what the expertise is of the reviewer, I would not know what I should think of the result.

Q Well, what if their result was contrary to what your opinions were in reviewing these slides?

A Again, I -- I -- I -- as long as I don't have information about the qualifications of the reviewer, I cannot say whether I would, you know, agree with those reviews or not.

Q Well, in terms of slides that you reviewed and came to opinions regarding those, I think on some occasions you said that if -- if the Takeda reviewer saw the slide contrary to your opinions, they got it wrong.

Do you remember questions about that?

A Can you repeat the question, please?

Q Sure.

You were repeatedly asked whether you thought the Takeda reviewer of these preclinical slides got it wrong when they reviewed these slides and came to their conclusions.

Do you remember that question?

A Yeah. I remember those questions.

Q Okay. So -- and why did you think that they -- you -- that they got it wrong if they came to opinions different than yours?

A I reviewed the slides. I made my diagnosis on these slides. They were not consistent with what the Takeda scientists reported.

I diagnosed acute tubular injury in all of these studies that I show in my report. And those lesions were, as far as I know, not described by the Takeda scientists. So this is why I disagree with them.

Q So if a -- an FDA scientist looked at the slides and came to conclusions similarly contrary to your conclusions, would you similarly disagree with them?

A Yes, I would.

Q For the same reasons?

A For the same reasons.

Q You -- you also were asked some questions about Dr. Perazella.

Do you remember that?

A Yes.

Q Okay. And I -- I --

MR. PENNOCK: Do you have that handy?

(Whereupon, there was a discussion off the record.)

BY MR. PENNOCK:

Q So I'd ask you to please tell me your opinion in terms of the respect that you have for Dr. Perazella.

A Dr. Perazella is a colleague of mine. He and I have published several papers together.

I would consider him an authority on drug-induced kidney injury, especially acute kidney injury. And I believe he has published one or two papers on PPI-induced acute interstitial nephritis.

Q Okay. And in terms of your views on his abilities to -- with regard to -- sorry.

In terms of your opinion of Dr. Perazella's abilities regarding drug-induced renal toxicity, could you please explain what your view is?

A I think that Dr. Perazella has published a body of knowledge on acute drug-induced kidney toxicity in patients. However, he has not, to my knowledge, published or has been -- or been involved in animal studies of toxicity.

So in that respect, I would consider myself more competent than him in judging animal studies.

And I'm also not aware that he has studied or published on PPI-induced acute tubular injury.

So in that respect, due to my review for this litigation, having reviewed thousands of slides, I think that I would probably be the more competent person at this very time point judging PPI-induced tubular injury in animals.

Q Nevertheless, do -- do -- is it your view that -- withdrawn.

Nevertheless, your -- your respect for Dr. Perazella, how would you characterize it? Very high?

A Very high. No.

Dr. Perazella is a colleague and very competent. So I would say that my respect for him is high.

Q And -- hang on one second, please.

(Whereupon, there was a discussion off the record.)

BY MR. PENNOCK:

Q In -- in -- in -- in coming to your opinions in -- in this case, Doctor, you did not only -- you did not only rely on what was written in the company's clinic -- preclinical study reports; is that true?

A In -- in respect to which position or --

Q Well, so throughout the last couple of days, different portions of the preclinical study reports were read to you and -- and you -- you had acknowledged that you had read those portions of the -- the reports or you had read the reports; right?

A Right. Right. Yes.

Q Okay. And were the reports themselves the only thing that you relied upon in coming to your opinions or did you look at other materials?

MR. MIZGALA: Form.

A So I looked at the reports. I looked at the expert reports of Dr. Levin and Sandusky. I also reviewed scientific articles, many of them.

So it was a, you know, variety of documents that I reviewed in preparation.

BY MR. PENNOCK:

Q And -- and also the slides themselves that you asked for?

A Of course, yes.

Q And -- and whatever was available to you?

A Right.

Q So were there any times in your review of the slides that you found in your analysis that

the slides contradicted what was reported in the preclinical study reports?

MR. MIZGALA: Form.

A I found that actually in several studies that what I saw on the slide differed from what was described in the study report.

BY MR. PENNOCK:

Q Is chronic progressive nephropathy -- withdrawn.

Do you have any recollection as to how Takeda defined chronic progressive nephropathy in rats?

A As far as I remember, they define progressive -- chronic progressive nephropathy as a spontaneous lesion that occurs predominantly in certain strains of male rats, that includes thickening of tubular basement membrane, tubular atrophy, interstitial fibrosis, thickening of the glomerular basement membrane, glomerulosclerosis, basophilia, casts.

And I think that pretty much sums it up.

Q And -- and what -- what was the -- withdrawn.

What, if any, views do you have

regarding Takeda's, in part, defining chronic progressive nephropathy in the rats as being spontaneous?

A Can you repeat that question, please?

Q Sure.

You mentioned that Takeda had -- that -- that there was a -- some notion of spontaneity or that the chronic progressive --

A Right.

Q -- nephropathy was spontaneous.

A Uh-huh.

Q What, if any, views do you have of that aspect of their definition?

A So I believe, from my review of the literature, that CPN cannot spontaneously occur in aging rats. And I think the molecular mechanisms underlying that process are not entirely clear. It may have to do with the genetics of the animal strain involved.

But from my review of the CPN literature, I believe that it is a -- in -- in the classic presentation, a spontaneous lesion in aging rats.

Q And after reviewing the slides that you've reviewed in this case --

A Uh-huh.

Q -- did you see such spontaneous lesions?

A So I did not see a classic CPN lesion as described in the literature and the textbooks in any of the slides that I reviewed.

I always saw an acute component, especially, of course, in the drugged animals, which in my opinion does not fit in the definition of chronic progressive nephropathy. You should not see acute tubular injury in chronic progressive nephropathy. You should not see dose-dependent increase and interstitial inflammatory infiltrate in chronic progressive nephropathy.

So the fact that I saw these acute injury features make me believe that these lesions are not chronic progressive nephropathy.

Q Okay. Should you see CPN in female rats?

A They're reported to be more common in male rats.

Q What about in Wistar rats?

A So I believe the Wistar rat is -- if my memory is correct, I believe the Wistar rat is not

a classic rat. I think the Fischer rat and the Sprague-Dawley rats are more the typical rats with CPN.

I hope I remember that correctly.

Q Okay. In terms of your -- your methodology for going about the review of the AstraZeneca slides and the Takeda slides, is that methodology set forth in your two reports?

A Yes. I describe my methodology in my reports.

MR. PENNOCK: Okay. I -- I don't have any further questions. I pass the witness back to James or Katherine, whoever wants to start.

MS. ALTHOFF: Nothing further for AstraZeneca. Thank you for your time, Dr. Moeckel.

THE WITNESS: Thank you.

MR. MIZGALA: Yup. That's a wrap. Thanks, Doc.

THE WITNESS: Thank you.

MR. PENNOCK: Thank you, everybody.

THE VIDEOGRAPHER: Off the record 4:16 p.m.

(Thereupon, the deposition was concluded at 4:16 p.m.)

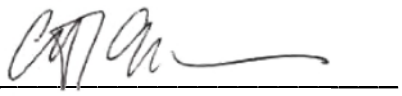
C E R T I F I C A T E

I, Clifford Edwards, Certified Shorthand Reporter, do hereby certify that prior to the commencement of the examination, the witness was duly remotely sworn by me to testify to the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a verbatim transcript of the testimony, that said deposition was taken by me stenographically at the time and date hereinbefore set forth, and the foregoing is a true and accurate transcript of the testimony.

I FURTHER CERTIFY that I am neither of counsel nor attorney to any of the parties to said suit, nor am I an employee of any party to said suit, nor of any counsel in said suit, nor am I interested in the outcome of said cause.

Witness my hand and seal as Notary Public this 13th day of July, 2021.



Clifford Edwards

Notary Public

My commission expires: 9/30/2021

J U R A T

I have read the foregoing pages and hereby acknowledge the same to be a true and correct record of the testimony.

_____

Gilbert W. Moeckel, M.D., Ph.D., FASN

Subscribed and sworn to

_____.

Before me this _____ day of _____, 2021.

_____

Notary Public

My Commission Expires:

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